INTRARENAL RESISTIVE INDEX AS A PROGNOSTIC PARAMETER IN PATIENTS WITH LIVER CIRRHOSIS COMPARED WITH OTHER HEPATIC SCORING SYSTEMS

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M.D GENERAL MEDICINE

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TAMIL NADU, INDIA

CERTIFICATE

This is to certify that the dissertation entitled "**INTRARENAL RESISTIVE INDEX AS A PROGNOSTIC PARAMETER IN PATIENTS WITH LIVER CIRRHOSIS COMPARED WITH OTHER HEPATIC SCORING SYSTEMS"** is the bonafide work of **Dr.P.ANAND** in partial fulfilment of the university regulations of the Tamil Nadu Dr.M.G.R Medical University, Chennai, for M.D General Medicine Branch I examination to be held in April 2018.

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DECLARATION

I, **Dr. P.ANAND,** solemnly declare that, this dissertation entitled **"INTRARENAL RESISTIVE INDEX AS A PROGNOSTIC PARAMETER IN PATIENTS WITH LIVER CIRRHOSIS COMPARED WITH OTHER HEPATIC SCORING SYSTEMS"** is a bonafide record of work done by me at the Department of General Medicine, Govt. Rajaji Hospital, Madurai, under the guidance of **Dr.R.BALAJINATHAN, M.D**, Professor, Department of General Medicine, Madurai Medical College, Madurai.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfilment of the rules and regulations for the award of **M.D Degree General Medicine Branch-I;** examination to be held in **April 2018.**

Place: Madurai

Date: **Dr. P.ANAND**

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INTRODUCTION

INTRODUCTION

Advanced liver cirrhosis is associated with a poor clinical outcome. Therefore, assessment of prognosis is important in the management of these patients. The Child-Pugh score has long been the most widely used specific scoring system in liver disease. In 2002, the Model for End-Stage Liver Disease (MELD) was introduced for patients undergoing transjugular intrahepatic portosystemic shunt. It is currently used to predict survival in patients awaiting liver transplantation. The MELD seems to be superior to the Child-Pugh score in prioritizing potential liver recipients according to mortality risk. However, it is only based on three laboratory variables, and thus does not take into account all prognostic factors that will impact on the survival of cirrhotic patients, notably complications due to portal hypertension. There is still a need for improvement of prognostic markers that could be easily integrated into the clinical management of these patients. Patients with liver cirrhosis frequently develop renal dysfunction. The hepatorenal syndrome (HRS), the most serious renal complication, is associated with an extremely short survival time.

The HRS is characterized by renal arterial vasoconstriction, which may precede clinically manifest renal dysfunction. The intrarenal resistance index (RI) is the most frequently used parameter to assess intrarenal resistance and is calculated based on Doppler sonographic intrarenal measurements. It is routinely used to diagnose transplant rejection or renal artery stenosis. The RI

is calculated as per the formula given below: (peak systolic frequency shift-lowest diastolic frequency shift)/peak systolic frequency shift.

On average, renal RI is higher in cirrhotic patients.The normal value of RI is 0.60-0.70 and is measured at the arcuate arteries (corticomedullary junction) or interlobar arteries (adjacent to medullary pyramids). Increased intrarenal RIs in patients with liver cirrhosis, especially in the decompensated stage, have been described before as compared to healthy controls. Cirrhotic patients with elevated intrarenal RIs tend to develop the HRS, leading to a poor prognosis. In the current study, we prospectively investigated the course of intrarenal RIs in patients with liver cirrhosis and compared its prognostic impact with those of the MELD and the Child-Pugh scores.

AIMS AND

OBJECTIVES

AIMS AND OBJECTIVES

1. To study the levels of renal resistive index in patients at various stages of liver cirrhosis.
2. To compare the values between patients with compensated and decompensated cirrhosis
3. To compare their prognostic impact with those of the Model for End-Stage Liver Disease (MELD) and the Child-Pugh scores.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Gross Anatomy

Embryologically, the liver grows as a ventral diverticulum from the junction of foregut and the midgut into the ventral mesogastrium (the caudal part of the septum transversum; the cranial part forms the diaphragm). The same diverticulum forms the gallbladder and bile ducts as well. The ligamentum teres hepatis is the obliterated umbilical vein, which joins the left portal vein; the ligamentum venosum is the obliterated ductus venosus, which joins the left portal vein to left hepatic vein.

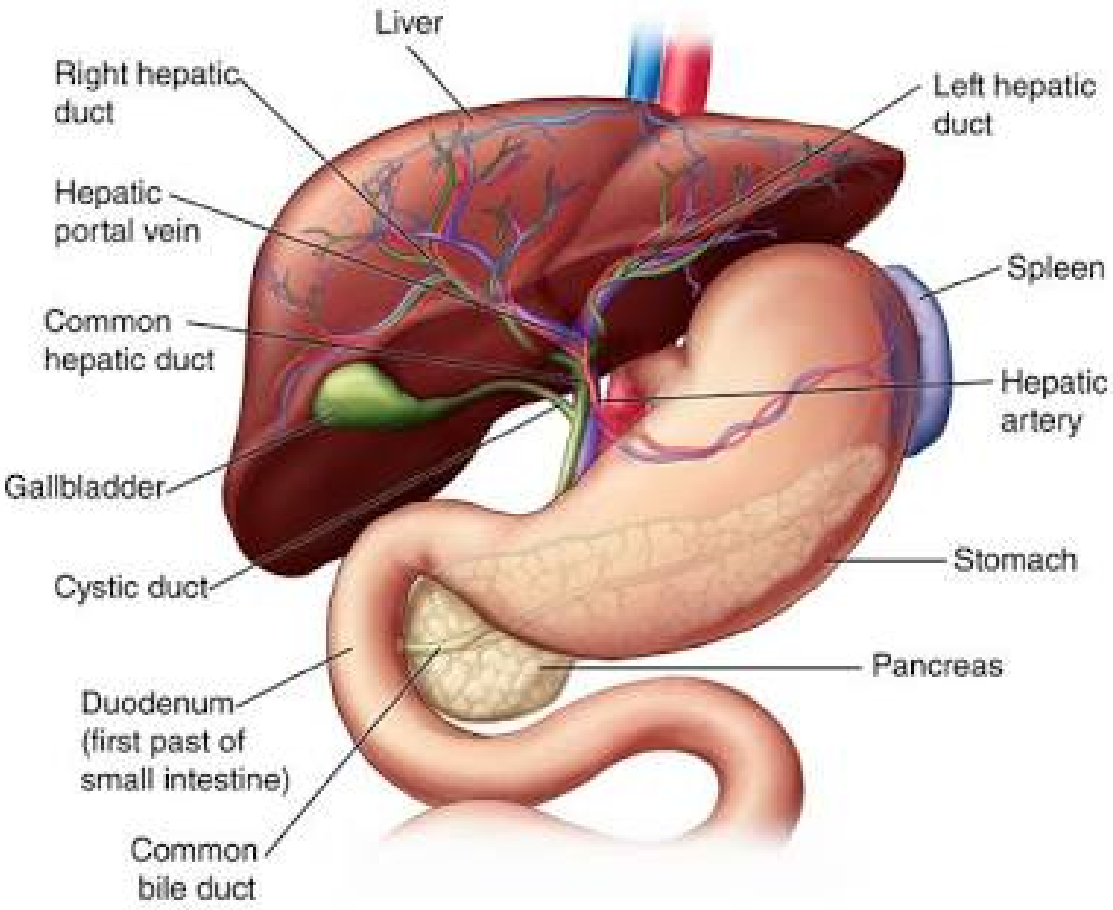
The upper surface of the liver is percussed at the level of the fifth intercostal space. Superior, anterior, posterior and right surfaces of the liver are continuous with each other and are related to the diaphragm and anterior abdominal wall.

The anterior surface is separated from the inferior (visceral) surface by a sharp anterior (inferior) border that is clinically palpable on deep inspiration. The inferior surface is related to the hepatic flexure (the area where the vertical ascending (right) colon takes a right-angle turn to become the horizontal transverse colon), right kidney, transverse colon, duodenum and stomach. The gallbladder straddles the undersurfaces of liver segments IVB and V.

There is an H-shaped fissure on the inferior surface of the liver. The right vertical arm of the H is formed by the gallbladder anteriorly and the inferior vena cava (IVC) posteriorly; it is incomplete, with the caudate process

between the two. The left vertical arm of the H is formed by the ligamentum teres hepatis in front and the ligamentum venosum behind.

The transverse limb of the H is the porta hepatis (hilum), a 5-cm transverse fissure (slit) on the undersurface of the liver with the quadrate lobe in front and the caudate lobe behind. It contains the common hepatic duct (CHD) in front and to the right, the proper hepatic artery in front and to the left, and the portal vein behind, enclosed in the hepatoduodenal ligament (HDL), composed of 2 layers of lesser omentum.



Anatomic Divisions

Anatomically, the liver is divided into a larger right lobe and a smaller left lobe by the falciform ligament (see the image below). This division, however, is of no use surgically. From a surgical point of view, the liver is divided into right and left lobes of almost equal (60:40) size by a major fissure (Cantlie's line) running from the gallbladder fossa in front to the IVC fossa behind. This division is based on the right and left branches of the hepatic artery and the portal vein (see the image below), with tributaries of bile (hepatic) ducts following. The middle hepatic vein (MHV) lies in Cantlie's line. The left pedicle (left hepatic artery [LHA], left branch of the portal vein, and left hepatic duct) has a longer extrahepatic course than the right. Each lobe is divided into 2 sectors. The right hepatic vein (RHV) divides the right lobe into anterior and posterior sectors; the left hepatic vein (LHV) divides the left lobe into medial (quadrate) and lateral sectors. While the falciform ligament and umbilical fissure mark the division between left lateral and left medial sectors on the surface of the liver, no surface marking is observed between right anterior and right posterior sectors. The posterior sector of the right lobe and the caudate lobe are not seen on a frontal view of the liver; the anterior sector of the right lobe forms the right lateral border in this view.

The sectors are further divided into segments (after Couinaud); each segment has its own blood supply and biliary drainage. The anterior sector of the right lobe contains superior (VIII) and inferior (V) segments. The posterior sector of the right lobe has superior (VII) and inferior (VI) segments. The

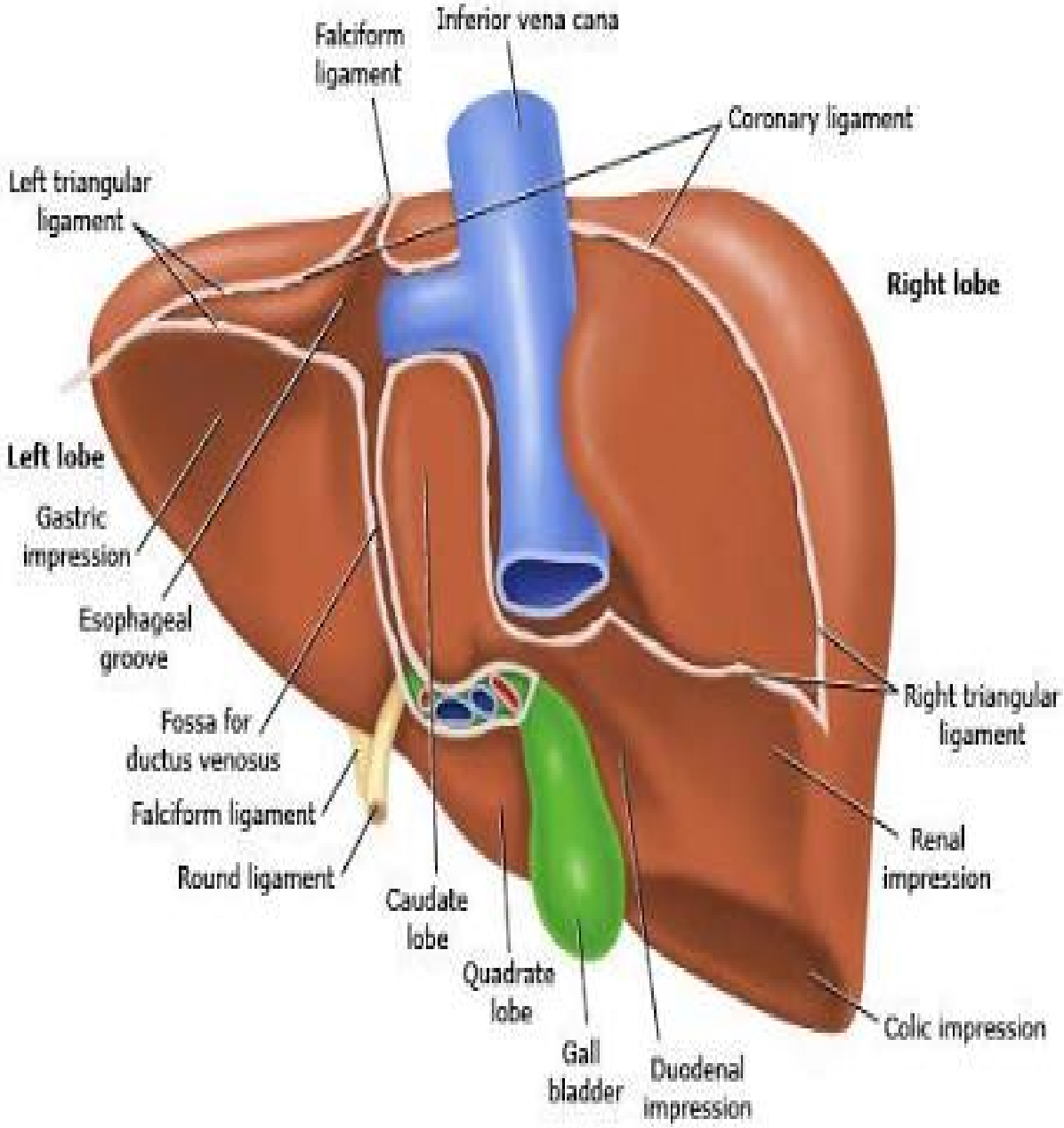
medial sector of the left lobe (quadrate lobe, segment IV) is part of the left lobe from a surgical perspective but lies to the right of the midline; it is further divided into a superior subsegment (A) and an inferior subsegment (B) (note: Japanese surgeons call the superior subsegment B and inferior subsegment A). The lateral sector of the left lobe contains segments II and III.

The caudate lobe (segment I) lies in the lesser sac on the inferior surface of the liver between the IVC on the right, the ligamentum venosum on the left, and the porta hepatis in front (see the image below). The caudate lobe has three parts: a left spigelian lobe, a paracaval part, and a caudate process that connects the caudate lobe to the right lobe. The caudate lobe receives numerous small branches from the right hepatic artery (RHA), the LHA, the portal vein, and the confluence; bile ducts drain similarly.

Caudate 'lobe' is not a lobe but a segment (I); left lateral 'segment' is not a segment but a sector including two segments (II and III).

On computed tomography (CT), the portal vein branches (with the left being higher than right) divide the right and left lobes of the liver into superior and inferior halves. The superior half of liver is composed of (from right to left) segments VII, VIII, IVA and II; the inferior half is composed of (from right to left) segments VI, V, IVB and III.

Accordingly, the right portal vein divides the posterior sector of the right lobe into segments VII (superior) and VI (inferior) and the anterior sector of the right lobe into segments VIII (superior) and V (inferior). The left portal vein divides the medial sector of the left lobe (quadrate lobe) into subsegments A (superior) and B (inferior) and the lateral sector of the left lobe into segments II (superior) and III (inferior).


Falciform ligament
Inferior vena cana
Coronary ligament
Left triangular ligament
Right lobe
Left lobe
Gastric impression
Esophageal groove
Fossa for ductus venosus
Falciform ligament
Round ligament
Caudate lobe
Quadrate lobe
Gall bladder
Duodenal impression
Right triangular ligament
Renal impression
Colic impression

Ligaments

The falciform ligament (which divides the liver into a larger anatomical right lobe and a smaller anatomical left lobe) has 2 layers of peritoneum; it attaches the anterosuperior surface of liver to the anterior abdominal wall and diaphragm. The free edge of the falciform ligament contains the ligamentum teres hepatis (round ligament of the liver): the obliterated umbilical vein, which is attached to the inferior surface of the liver between segment IV on the right and segment III on the left. The ligamentum venosum (the obliterated ductus venosus) is attached to the inferior surface of the liver between the caudate lobe and the left lateral sector.

The superoposterior surface of the liver has coronary and left triangular ligaments; between the 2 leaves of the coronary ligament to the right of the IVC is the bare area of the liver, which is in contact with the inferior vena cava and inferior surface of the diaphragm. The falciform ligament is continuous with the anterior layer of the coronary ligament. On the left, the anterior and posterior layers of the coronary ligament unite to form the left triangular ligament. On the right, the anterior and posterior layers of the coronary ligament unite to form the right triangular ligament.

The posterior layer of the coronary ligament on the right side is called the hepatorenal ligament. The hepatorenal pouch is the area below the posterior layer of the right triangular and coronary ligament over the right kidney. The lesser omentum connects the liver with the lesser curvature of the stomach and the first part of the duodenum via hepatogastric and hepatoduodenal ligaments.

Inferior vena cava ligament is a bridge of tissue between posterior surface of right lobe and caudate lobe behind the inferior vena cava.

Blood Supply

The liver has a unique dual blood supply (about 1500 mL/min) both from the proper hepatic artery (20-40%) and from the portal vein.

The celiac trunk (axis) comes off the anterior surface of the abdominal aorta at the level of T12 – L1 between the right and left crura of the diaphragm. It is a short structure (about 1 cm) that trifurcates into the common hepatic artery (CHA), the splenic artery, and the left gastric artery (LGA).

The CHA runs toward the right on the superior border of the proximal body of the pancreas. After giving off the gastroduodenal artery (GDA) behind the first part of the duodenum above the neck of the pancreas, it continues as the proper hepatic artery in the HDL (the free edge of the lesser omentum) to the left of the bile duct and in front of the portal vein. In the hepatic hilum, it divides in a Y-shaped manner into the RHA and the LHA, with the RHA ascending behind the CHD; the cystic artery is usually a branch of the RHA.

The portal vein, formed by union of the superior mesenteric vein (SMV) and the splenic vein behind the neck of the pancreas, collects blood from the gastrointestinal (GI) tract (SMV and inferior mesenteric vein [IMV]) and from the spleen and pancreas (splenic vein). It then ascends in the HDL behind the CBD and the proper hepatic artery and divides in a T-shaped manner into right and left portal vein branches in the hepatic hilum. The right portal vein divides

within the liver parenchyma into a vertical right anterior sectoral branch (which then divides into segmental V and VIII branches) and a horizontal right posterior sectoral branch (which then divides into segmental VI and VII branches). The left portal vein runs below the base of segment IV to which it gives off several small branches; it then enters the liver parenchyma where it divides into branches to segments IV, III, and II.

The hilar plate is a condensation of fibroareolar tissue that lies on the undersurface of the hilum of liver, separating it from the biliovascular pedicle at the porta hepatis; it continues along the right and left portal pedicles as sleevelike sheaths.

The left portal vein connects to the umbilical vein through the ligamentum teres hepatis and to the left hepatic vein through the ligamentum venosum. The portal venous system (2 groups of capillaries, one in the organ being drained and the other in the liver) has no valves.

Portosystemic connections are present in the gastroesophageal area (between the esophageal tributary of the left gastric vein and the esophageal tributaries of the azygos vein), in the rectum (between the superior, middle, and inferior rectal veins), around the umbilicus (between the left portal, umbilical, and paraumbilical veins and the superficial and deep epigastric veins), and in the retroperitoneum (between the colic and splenic veins and renal and posterior parietal veins).

The three hepatic veins (RHV, MHV, and LHV) are largely intrahepatic and lie on the posterior surface of the liver. The MHV and the LHV may join

to form a common trunk before draining into the IVC. The IVC lies on the posterior surface of the liver in a groove (or, sometimes, a tunnel) between the bare area on the right, the caudate lobe on the left, and the caudate process in front.

CT Anatomy

On contrast-enhanced CT scanning, the right hepatic vein (horizontal) lies between the right posterior sector and right anterior sector; the middle hepatic vein (vertical) lies between right anterior sector and segment IV; and the left hepatic vein lies between left medial sector and left lateral sector. Portal vein bifurcation into right and left branches separates the cranial segments (VII, VIII, IVa, II) from the caudal segments (VI, V, IVb, III).

Microscopic Anatomy

The surface of the liver is covered by visceral peritoneum (serosa), with a Glisson capsule underneath. At the porta hepatis, the Glisson capsule travels along the portal tracts (triads), carrying branches of the hepatic artery, the portal vein, and the bile ducts into the liver substance.

Sinusoids are large-diameter capillaries lined by endothelial cells between rows of plates or cords of hepatocytes. Sinusoids also contain Kupffer cells of the reticuloendothelial system (RES). Each hexagonal lobule has a central portal tract with branches of the hepatic artery, the portal vein, and bile ducts, as well as a peripheral tributary of the hepatic vein. Bile canaliculi between hepatocytes drain into bile ductules in the portal triad. Bile ductules

then form several orders of intrahepatic bile ducts, in an arrangement resembling the twigs and branches of a tree.

The left portal pedicle lies at the base of segment IV and has a long extrahepatic course. The right portal pedicle has a short extrahepatic course; it divides into a right anterior sectoral pedicle which lies in the gallbladder fossa and a right posterior sectoral pedicle, which lies in the Rouviere sulcus.

In cirrhosis, the superoinferior span (between the upper percussible border and the lower palpable border) of the liver, which is normally 12-16 cm, is reduced. Caudate lobe hypertrophies can occur in cirrhosis.

Lobar, sectoral, and segmental liver resection (ie, lobectomy, sectorectomy, and segmentectomy) can be performed (eg, right hepatic lobectomy [segments V-VIII], left hepatic lobectomy [segments II-IV], right posterior sectorectomy [segments VI, VII]). Liver lobes (right or left) can be removed from a live donor and transplanted to another person. Intraoperative ultrasonography may delineate intrahepatic blood vessels (eg, hepatic artery, portal vein, and hepatic vein) and bile ducts and is a very useful tool for liver resections.

Liver has enormous capacity of regeneration; normal liver can tolerate major liver resections involving up to 70-75% of liver parenchyma.

Liver cancer (hepatocellular carcinoma) drains into hepatic lymph nodes at the porta hepatis and into the lymph nodes in the hepatoduodenal ligament.

A hepatocellular carcinoma is supplied mainly by the hepatic artery. Unresectable tumors can be treated with transarterial embolization (TAE),

transarterial chemo-embolization (TACE), and transarterial radio embolization (TARE).

The liver has a dual (arterial and portal) blood supply. The hepatic artery can be ligated or embolized; the liver then gets its arterial blood supply from the diaphragm and abdominal wall through its ligaments and the bare area.

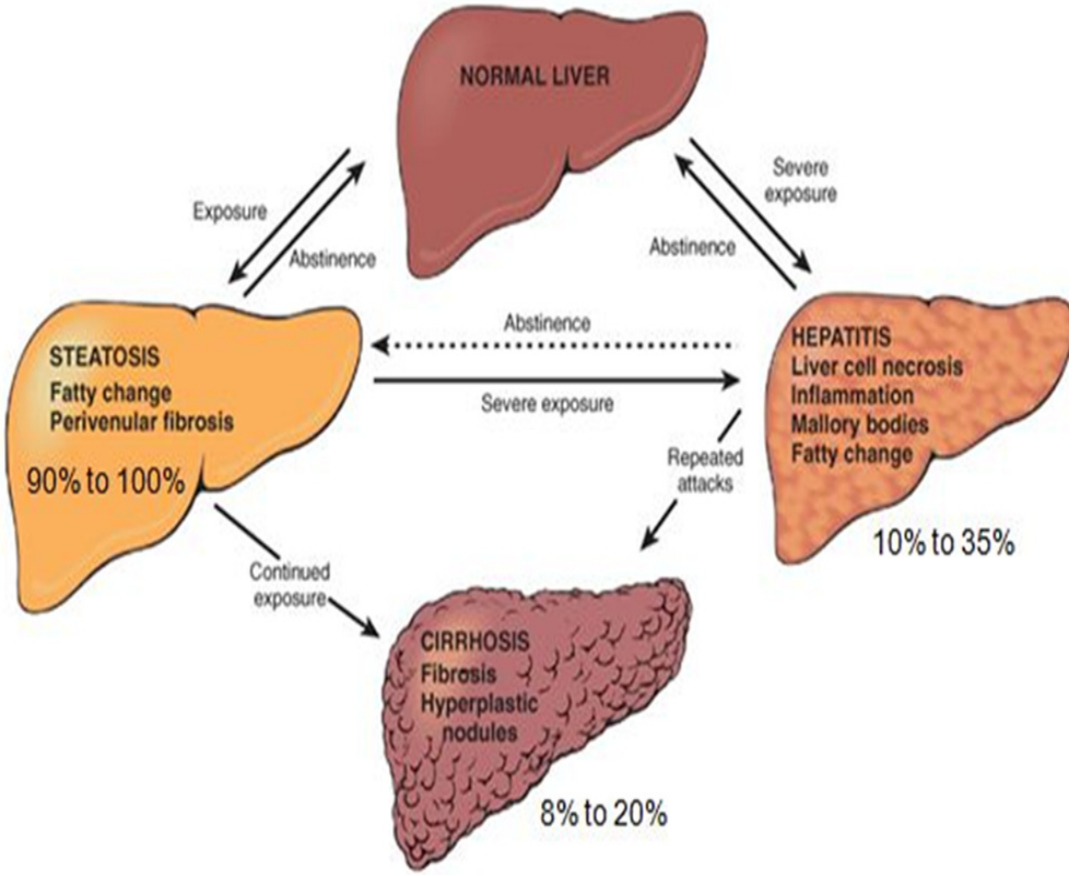
Unilateral portal vein embolization results in atrophy of ipsilateral lobe and hypertrophy of contralateral lobe. This is useful before major liver resections to increase the functional liver remnant (FLR).

Cirrhosis of liver

Cirrhosis of liver is a continuous, progressive and anatomically diffuse process characterized by fibrosis and distortion of the liver parenchyma with formation of nodules, resulting in decreased function of the liver and increased resistance to flow of portal venous blood .This process of cirrhosis is generally irreversible in the late stages and liver transplantation is the only treatment option in the advanced stage. But it is to be noted that certain conditions causing cirrhosis may respond to treatment of the underlying cause even resulting in reversal of the process in the early stages .This peculiarity is seen in cirrhosis caused by hepatitis C, alcohol, iron overload and obesity.

Cirrhosis is the end stage of chronic injury, inflammation and destruction and regeneration of the hepatocytes, inflicted by various conditions. The pathological features include the development of excessive

fibrosis along with nodular regeneration of the parenchyma, fmally culminating in complete alteration in the architecture, and blood flow through the liver. The induction of the process of fibrosis occurs with the" activation of hepatic stellate cells, leading to the formation of increased amounts of collagen and other extracellular matrix components". As the function progressively decreases and portal hypertension develops secondary to the altered portal blood flow, various complications of cirrhosis set in and the survival of the patients is very much shortened.



In India and most of the developing countries, the most common etiologies for development of cirrhosis are:

1. Alcoholic liver disease
2. Viral hepatitis.

Whereas in developed countries the common causes include:

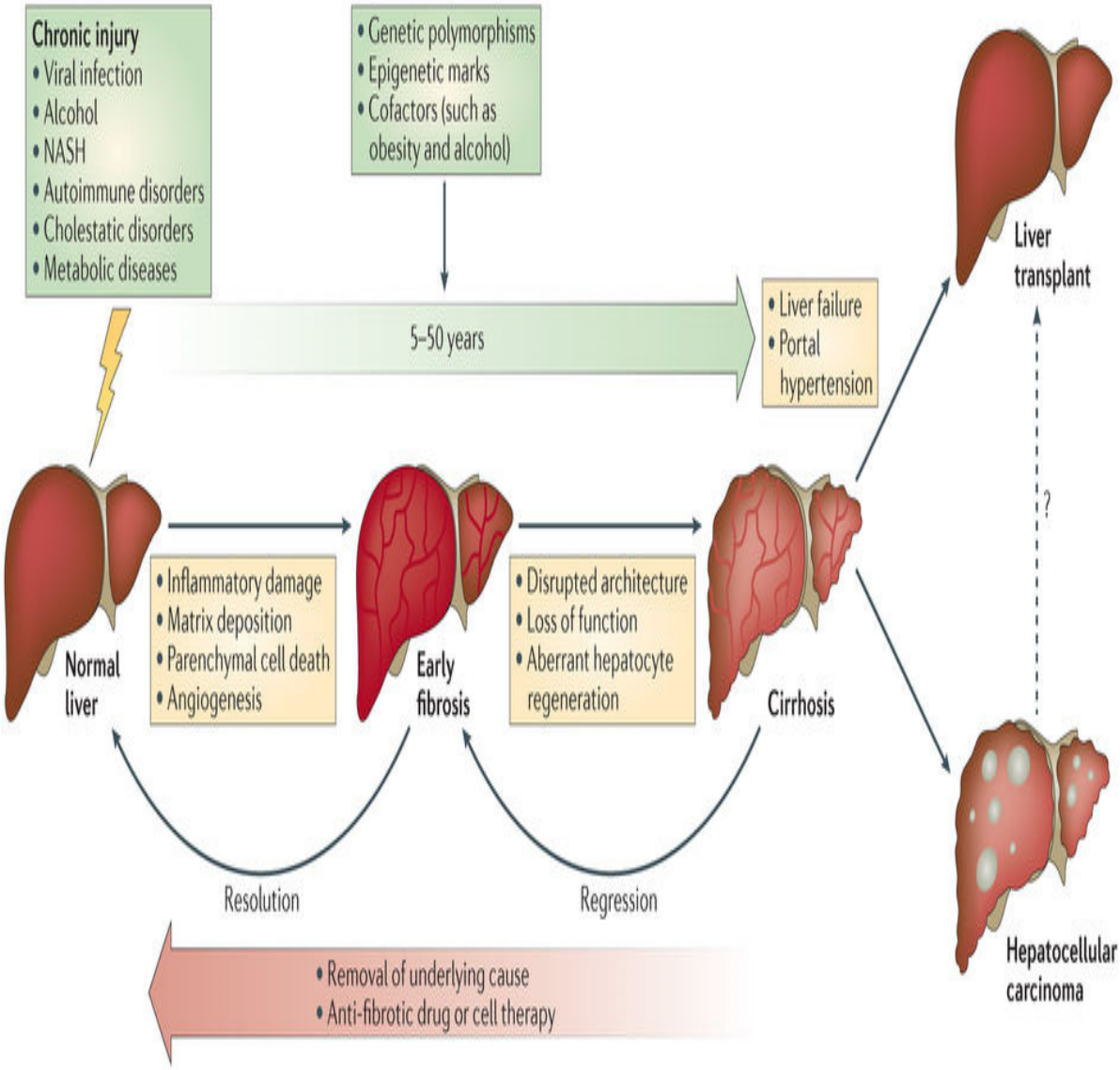
- Nonalcoholic fatty liver disease
- Alcoholic cirrhosis
- Viral cirrhosis (hepatitis C)
- Other less frequent causes include:
- Primary and secondary biliary cirrhosis
- Autoimmune hepatitis
- Primary sclerosing cholangitis
- Wilson disease
- Hemochromatosis
- Type 4 glycogenosis
- Alpha-1 antitrypsin deficiency
- Galactosemia
- Tyrosinemia
- Idiopathic portal fibrosis

- Infection (e.g., brucellosis, syphilis, echinococcosis, schistosomiasis)
- Polycystic liver disease
- Right-sided heart failure
- Veno-occlusive disease

In some forms of liver disease, only a single etiological agent is responsible for development of cirrhosis such as in chronic viral hepatitis (hepatitis B and C and primary biliary cirrhosis. But in most of the cases additional cofactors also contribute to the progression to cirrhosis. For example, of the people with homozygous mutations of C282Y for hemochromatosis only a small fraction develop cirrhosis. Other factors such as age, sex, alcohol, obesity, iron intake may play a major role. Similar is the case with alcoholic liver disease and NASH. Causes of cirrhosis also interact Progression to cirrhosis happens in shorter duration in patients with hepatitis B or C who also drink excess alcohol. Age of the patient, immunological status, duration of the disease are other factors affecting the progression to cirrhosis.

PATHOGENESIS

"Induction of fibrosis occurs with activation of hepatic stellate cells to myofibroblasts resulting in the development of increased amounts of collagen and other components of the extracellular matrix leading to architectural distortion inturn resulting in decrease in function and mass."



CLINICAL MANIFESTATIONS

Patients may present to the clinic for the first time with the complications of cirrhosis or may be asymptomatic and incidentally be identified during medical checkup for unrelated causes or because of abnormal liver function tests.

In clinical terms, cirrhosis is classified in to

- Compensated form and
- Decompensated form.

Decompensation is characterized by cirrhosis complicated by one or more following features like - jaundice, ascites, hepatic encephalopathy, bleeding varices. Ascites is usually the first sign of decompensation. Whereas these features and any complication secondary to portal hypertension is absent in compensated cirrhosis. This distinction clinically is very important because of the implication it has in the prognostication and treatment. Compensated cirrhosis patients have a ten year survival rate of 50% whereas decompensated patients have a survival rate of about 50% in 18 months. A decompensated patient may become compensated when the inciting cause or the precipitating cause is removed and thereby the prognosis may improve.

COMPENSATED CIRRHOSIS

At this stage, the cirrhotic process of the liver is not severe enough to alter the function significantly and so the patients may asymptomatic or present with non-localizing manifestations or may be picked incidentally due to alteration in biochemical parameters or imaging studies .Patients may have fatigue, anorexia, weight loss, flatulence dyspepsia, abdominal pain. On examination, palmar erythema, pedal edema, spider naevi, may point towards cirrhosis. Abdominal examination may reveal an epigastric mass which is the enlarged left lobe of the liver and splenomegaly. Biochemical tests are usually

within normal limits in this group. The most common LFT abnormality in this group include mildly elevated transaminases, or GUT. Confirmation is by liver imaging or liver biopsy. Factors like bacterial infection, trauma, or medications, surgery may precipitate decompensation in compensated cirrhosis

DECOMPENSATED CIRRHOSIS

These patients present with ascites, jaundice, altered sensorium, bleeding manifestations.

SYMPTOMS

Presentation in these patients may be with features of jaundice, pedal edema, abdominal distension, Upper GI bleed most commonly melena, hematemesis, pruritus, altered sensorium ranging from sleep disturbances to florid confusion and coma because of hepatic encephalopathy. In women, menstrual irregularities are common due to anovulation .Men, may manifest hypogonadism in the form of impotence, loss of sexual drive, testicular atrophy and infertility.

GENERAL EXAMINATION

Decreasing blood pressure - with progression of cirrhosis, mean arterial pressure often decreases. Hypertensive patients may become normotensive.

Patients can have mild fever (37.5 -38 C). This is probably because of bacteremia due to gram negative organisms. Ongoing hepatocyte necrosis, development of hepatocellular carcinoma may also contribute.

Jaundice (This happens once the functional impairment due to hepatocyte destruction has exceeded the process of regeneration. The deeper the jaundice, more severe is hepatic decompensation)

Skin findings

Bronze pigmentation of the skin may throw light on the etiology as it occurs in hemochromatosis.

Presence of vascular spiders (arterial spiders/ spider naevi/ spider telangiectasia/ spider angioma). They are seen in distribution of venous drainage areas of superior vena cava. As liver function worsens, new spiders may appear. They are more frequently associated with alcoholic cirrhosis. They occur normally in pregnancy and in some normal individuals. Hepatopulmonary syndrome is characterized by multiple spiders and clubbing.

Palmar erythema: palms are warm and red in colour especially over the thenar eminence, hypothenar eminence and the pulp of the fingem.

Mechanism of both arterial spiders and palmar erythema may be due to estrogen excess. The estrogens are inactivated in the liver. Even though serum estradiol level is normal and serum free testosterone is reduced. Thus the high estradiol/free testosterone ratio may be attributed to these findings.

Leukonychia (related to hypoalbuminemia)

Clubbing can occur pan digitally especially with development of hepato pulmonary syndrome or in cystic fibrosis .Hypertrophic osteoarthropathy has also been observed.

Dupuytrens contracture may be present. This is characterized by thickened palmar fascia resulting from unorganized proliferation of the fibroblasts.

Head and neck findings — Parotid enlargement, alopecia, fetor hepaticus, KF ring in the eyes due to Wilson's disease may be present.

Fetor hepaticus refers to the breath of the cirrhosis patients that has a sweet pungent nature. This is because of presence of mercaptans.

Chestfindings - Gynecomastia in males may be seen along with other features of feminization like change in the male pattern of pubic hair, loss of axillary hair and chest hair. It is because the androstenedione that is synthesized by the adrenals gets aromatized in to estrone and finally in to estradiol in the adipose tissue.

Abdominal findings - Abdominal examination may reveal the presence of ascites, hepatomegaly, splenomegaly. and dilated abdominal wall veins.

Ascites - Ascites refers to excessive collection of peritoneal fluid .In massive ascites fluid thrill may be present where as in moderate ascites shifting dullness is to be elicited. If flanks are full it is probably due to ascites and not fat.

Hepatomegaly - The cirrhotic liver may be enlarged, shrunken or normal sized. On palpation, consistency is firm and nodular. Features such as shape, consistency, tenderness are better appreciated on palpation as the estimation of liver size correlates less accurately with imaging studies. Presence of a palpable liver in cirrhosis usually signifies, alcoholic liver disease, primary

biliary cirrhosis hemochromatosis, transformation into hepatocellular carcinoma, Budd Chiari syndrome.

Splenomegaly - Splenomegaly in cirrhosis is due to congestion resulting from portal hypertension .However, correlation between splenic size and portal pressure is poor implicating that there may be other contributing.

Caput medusa - With the development of portal hypertension, the portal venous blood gets carried through the periumbilical veins in to the umbilical vein which becomes patent in cirrhosis .From there the blood drains in to the upper and lower abdominal veins that end up in systemic circulation .These veins become engorged and prominent .Thus the portal blood gets shunted to systemic circulation. This appearance resembles the head (caput) of the mythical Gorgon Medusa thus termed caput medusae.

Dilated abdominal veins developing in SVC obstruction and IVC obstruction should be differentiated from dilated veins due to cirrhosis. In order to distinguish the cause of obstruction direction of flow is to be assessed. In IVC obstruction the flow is below upwards whereas in cirrhosis the flow of the blood is away from the umbilicus. However since these veins in both conditions may lack valves, the flow may be bidirectional and the test may be misleading. Moreover the dilated veins due to obstruction are more commonly seen in the back and loin

Peptic ulcers occur in 11% of cirrhosis patients. Duodenal ulcers are more frequently encountered than gastric ulcers. Colonization by helicobacter pylori is higher in cirrhosis when compared to normal population. Abdominal

hernias are more common in patients with ascites. They should be repaired only if severe enough to cause mortality in alcoholics, associated chronic pancreatitis can be present which may relapse .So this should be considered a differential diagnosis in alcoholic cirrhosis presenting with abdominal pain.

Neurologic findings - The presence of Asterixis or liver flap indicate the presence of hepatic encephalopathy.

Genitourinary findings - Testicular atrophy in males.

Endocrine changes

Hyperglycemia occurs in about 80% of cirrhotic patients in the form of glucose intolerance. Only around 10-20% are hut diabetic.

INVESTIGATIONS

Liver function test abnormalities:

Aminotransferases - In chronic hepatitis, ALT is increased more than AST .As hepatitis progresses to cirrhosis, AST becomes more elevated than ALT and thus the ratio of AST to ALT is reversed from <1 to greater than 1 .In cirrhosis patients the enzymes can.be within normal values or may become moderately elevated.

- Alkaline phosphatase - Alkaline phosphatase enzyme is elevated 2 to 3 times normal in cirrhosis. If elevated more than that, primary biliary cirrhosis or sclerosing cholangitis should be considered as the etiology.

- Gamma-glutamyl transpeptidase - Levels of GGT and alkaline phosphatase are usually proportionately elevated Disproportionately high levels of GUT will be seen in alcoholic liver disease. GUT present in the microsomes gets induced due to alcohol intake.
- Bilirubin - In compensated stage of cirrhosis, the bilirubin levels are usually normal. Decompensation is characterized by increasing levels of bilirubin and it is one of the prognostic indicators used in Child Pugh score.
- Albumin - Albumin is exclusively synthesized in the liver. With worsening cirrhosis, due to the decline in the synthetic function of the liver, albumin levels also fall. It is also one of the prognostic indicators for survival in child scoring system.
- Prothrombin time - Most of the coagulation factors are synthesized in liver. Prothrombin time which measures the extrinsic coagulation pathway, is a marker for the synthetic function of the liver. Thus coagulopathy worsens as cirrhosis progresses.

Serum electrolytes - Hyponatremia can occur in patients with ascites. Severity can be correlated with worsening cirrhosis.

Hematologic abnormalities - Thrombocytopenia, anemia and leucopenia can occur. The earliest abnormality to occur is thrombocytopenia and it is a marker for the development of portal hypertension. Pancytopenia can even be the presenting feature in asymptomatic compensated cirrhosis. This is

sequestration of the cells in the enlarged spleen. Platelet count usually does not fall below 50,000.This does not per se cause bleeding but bleeding can get aggravated in the presence of coagulopathy

Anemia in cirrhosis is mainly because of upper GI bleed. Anemia can also be present as a result of direct suppression of bone marrow by alcohol, sequestration and hemolysis, folate deficiency.

Other abnormalities - In cirrhosis, the globulin levels are high. This is because of shunting of bacterial antigens in the portal venous blood which are normally filtered by the liver in to systemic circulation leading to induction in production of immunoglobulins. Marked elevations of IgG may point towards the presence of autoimmune hepatitis.

Imaging studies: Cirrhosis can be diagnosed radiologically using ultrasound, portal vein Doppler, CT and MRI in specific cases.

- Ultrasonography - Ultrasonography is a non-invasive routinely used investigation to diagnose cirrhosis. The size of the liver, the nodularity, the portal vein diameter, presence of ascites and splenomegaly can be assessed. Doppler studies to check the direction of blood flow in the portal vein aids in the diagnosis of portal hypertension. Presence HCC, portal vein thrombosis can also be made out.
- CT is not the first choice in the diagnosis of cirrhosis.It may be useful when investigating liver malignancy or secondaries or pancreatic pathology.

- MRI may be useful in hemochromatosis to reveal iron overload. MRA can determine portal vein flow and dynamics
- Elastography to assess the stiffness of the liver tissue is available.

Liver biopsy

The gold standard investigation for diagnosing cirrhosis is liver biopsy. Nowadays liver biopsy is rarely required to diagnose cirrhosis.

Only certain situations may require performing liver biopsy such as for demonstrating the underlying metabolic cause of cirrhosis such as NASH, Wilson disease, hemochromatosis, and alpha 1 antitrypsin deficiency

PROGNOSIS

Child-Turcotte-Pugh Score (CTP): This simple scoring sys:n widely in use in clinical practice, for predicting the prognosis and nsiSkw from the major complications of the cirrhosis patients. Even though it derived based on statistically significant studies and is only derived in n empirical manner, this score can predict the outcomes in patients with hvdr cirrhosis with reasonable accuracy.

The parameters included are:

Child-Turcofte-Pugh Classification for Severity of Cirrhosis			
	Points*		
	1	2	3
Encephalopathy	None	Grade 1-2 (or precipitant induced)	Grade 3-4 (or chronic)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	<2	2 - 3	>3
Albumin (gfdL)	>3.5	2.8 – 3.5	<2.8
INR	<1.7	1.7 – 2.3	>2.3
Class A = 5 to 6 points (least severe liver disease)			
Class B = 7 to 9 points (moderately severe liver disease)			
Class C 10 to 15 points (most severe liver disease)			

Initially this scoring system was used in the stratification of patients in to risk groups before taking them up for portosystemic shunt surgeries. Then in clinical practice this system was used to prioritize the patients to be taken up for liver transplantation (Child Pugh class B) but now this system has been replaced by MELD score for selection of patients for liver transplantation.

Model for End-stage Liver Disease (MELD)

MELD score is a score derived methodologically in order to prognosticate the patients with cirrhosis and portal hypertension. This score is calculated based on three noninvasively obtained variables: serum bilirubin, serum creatinine and INR.

Model for End Stage Liver Disease (MELD) Score
MELD = 3.78 x Iog serum bilirubin (mg/dL) + 11.20 X 109e INR + 9.57 x loge serum creatinine (mg/dL) + 6.43 (constant for liver disease etiology)
NOTES • If the patient has been dialyzed twice within the Iast 7days,then the value for serum creatinine used should be 4.0 • Any vaIue less than one is given a value of 1 (ie. if bilirubin is 0.8,a value of 1.0 is used) to prevent the occurrence of scores below 0

Patients with cirrhosis are given priority for liver transplantation on this particular score in the United States. Patient with a score more than 10 is to be considered for liver transplantation. This scoring system has the advantage that it is completely objective for assessment of severity of the disease and does not result in inter observer variation. Moreover the score has a wider range of values and thereby severity can be graded more precisely.

MAJOR COMPLICATIONS OF CIRRHOSIS

With the progression of cirrhosis and development of portal hypertension. Various complications occur as a result of either the decreased

synthetic. Excretory, metabolic functions of the liver and also some secondary to portal hypertension. The various complications include.

“Portal hypertension	Coagulopathy
Gastroesophageal varices	Factor deficiency
Portal hypertensive gastropathy	Fibrinolysis
Splenomegaly, hypersplenism	Thrombocytopenia
Ascites	Bone disease
Spontaneous bacterial peritonitis	Osteopenia
Hepatorenal syndrome	Osteoporosis
Type 1	Osteomalacia
Type 2	Hematologic abnormalities
Hepatic encephalopathy	Anemia
Hepatopulmonary syndrome	Hemolysis
Portopulmonary hypertension	Thrombocytopenia
Malnutrition	Neutropenia”

PORTAL HYPERTENSION

Portal hypertension is defined as “the elevation of the hepatic venous pressure gradient (HVPG) to >5 mmHg”.

Portal hypertension occurs as a result of two processes happening simultaneously:

1) The altered architecture of the liver due to fibrosis and regenerating nodules, results in increased resistance to the flow of the portal blood

2) Increased blood flow secondary to splanchnic vasodilatation

This portal hypertension results in variceal bleeding and ascites. The causes of portal hypertension are divided into pre-hepatic, post hepatic and intra-hepatic causes. Pre-hepatic causes are thrombosis of portal vein and splenic vein thrombosis which results in development of sinistral hypertension or left sided portal hypertension. Post hepatic causes are those affecting the hepatic veins and venous drainage in to the heart. Conditions include Budd Chiari syndrome veno occlusive disease, constrictive pericarditis, chronic right sided congestion, restrictive cardiomyopathy. Intra-hepatic causes include pre – sinusoidal causes such as schistosomiasis, congenital portal fibrosis and post sinusoidal causes including veno-occlusive disease and cirrhosis causes sinusoidal form of portal hypertension.

Clinically significant portal hypertension occurs in around 60%of cirrhosis patients. Portal vein thrombosis can occur secondary to cirrhosis per

se, pancreatitis, abdominal trauma and infection or hematological causes such as essential thrombocytosis, polycvthemia vera, Protein C and S deficiency.

The primary complications of portal hypertension include ascites, bleeding varices and hypersplenism.one third of the patients with cirrhosis have gastric and oesophageal varices. Thus it has become mandatory to screen all patients with established cirrhosis for the presence of varices using upper GI endoscopy. The risk of variceal bleed depends on several factors like the varices size, severity of cirrhosis, tense ascites, and increased wedged hepatic vein pressure. In patients with liver cirrhosis the development of portal hypertension may be revealed by the presence of thrombocytopenia, appearance of an enlarged spleen, encephalopathy, development of ascites and esophageal varices with or without bleeding. CT or MRI abdomen can be performed in doubtful cases or interventional radiological procedure to determine the free and wed hepatic vein pressure and the gradient between the two can be fbund out It is normally 5 mm Hg and if more than 12 mm Hg it signifies increased risk of bleeding. Once bleeding occurs acute therapy is to arrest the bleed and then followed by prophylaxis against repeated bleeding. Acute management is with intravenous fluids and blood products and use of octreotide at a rate of 50-100 mic/hour. This is followed by endoscopic variceal band ligation till the varices are obliterated. Non selective beta-blockers can be used as medical prophylaxis. If failing this mode of management, TIPS can be fried.

Splenomegaly results from congestion due to increased portal pressure. Hypersplenism with development of thrombocytopenia may be the first presentation of portal hypertension even before ascites may develop.

ASCITES

Ascites occur as result of excessive accumulation of peritoneal fluid. It can be because of cirrhosis per se or may be due to spontaneous bacterial peritonitis or development of malignancy.

Pathogenesis

The following mechanisms contribute to the occurrence of ascites in cirrhosis with portal hypertension.

The intrahepatic resistance is increased, causing increased portal pressure accompanied by vasodilatation in splanchnic arterial system due to release of vasodilatory substances such as nitric oxide. Resulting in increased portal inflow. Both these mechanisms cause increased production of splanchnic lymph. Intravascular volume depletion occurs due to splanchnic vasodilatation resulting in under filling in other vascular beds and this leads to increased activity of the renin angiotensin system .This leads to an increased release of aldosterone leading to sodium and water retention and thus peripheral edema and ascites. Decreased oncotic pressure due to hypoalbuminemia also contributes. Ascites may lead to hepatic hydrothorax also.

When patients present with ascites for the first time, diagnostic paracentesis is to be done. In patients with cirrhosis the ascitic protein content in the ascites is very low, less than 1.1 g/dl. SAAG ratio ('serum to ascites albumin gradient') has now replaced the description of exudate or transudate. A SAAG ratio of more than 1.1 g/dl denotes that the cause of the ascites is due to portal hypertension. If less than 1.1 g/dl infection or malignancy has to be ruled out. Risk of SBP is high when the ascetic fluid protein content is very low. Presence of RBCs indicates the presence of malignancy, omental varices or traumatic tap. Ascitic fluid polymorphonuclear cell count, of more than 250 cells/mic L indicates the presence of infection.

Patients with small amount of ascites are usually managed with restriction of salt in the diet. Patients should be advised to take not more than 2 gram per day and avoidance of preserved foods. Patients with moderate ascites are treated with diuretics. Spironolactone is started at a dose of 100-200 mg/day as a single dose and frusemide can be additionally prescribed at a dose of 40-80mg when peripheral edema is present. Dose of spironolactone can be escalated up to a dose of 400-600 mg and furosemide may be increased to 160 mg till clinical response occurs. If ascites is still present with these dosage of diuretics and on a sodium compliant diet, the term refractory ascites is used. Treatment of refractory ascites or repeated large volume ascites is with intravenous albumin infusion and TIPS. Recent studies have showed that TIPS useful in managing ascites but has no mortality benefit. Once resistant ascites

develops the prognosis is bad, with survival rates not more than 50% at the end of two years.

SPONTANEOUS BACTERIAL PERITONITIS

SBP can occur in patients with cirrhosis and ascites due to infection of the ascitic fluid without an intraabdominal source, spontaneously. The bacteria may translocate from the intestines in to the mesenteric lymph nodes followed by bacteremia and seeding of ascites may be the mechanism behind SBP. Escherichia coli is the commonest organism cultured. Streptococcus viridians, enterococcus and staphylococcus aureus and other gram positive bacteria can also cause SBP. Usually SBP is monobacterial, if polymicrobial - perforation of viscus is to be considered. The diagnosis of SBP is made when absolute

neutrophil count in the ascites is more than 250/micro liter .Patients presenting with fever, sudden increase in ascites, abdominal pain, and altered sensorium should be screened for SBP. Sometimes they may present without any of these features also. Treatment is with second generation cephalosporins. Prophylaxis 1kw SBP is given to patients with prior history of SBP, very low proteins in ascitic fluid and in patients with upper GI bleeding. Once weekly antibiotic is given as prophylaxis.

IIEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is otherwise called portosystemic encephalopathy. This is a complex syndrome of neuropsychiatric

manifestations with disturbances in conscious level and personality changes which fluctuate from day to day occurring either in chronic liver disease or fulminant hepatic failure. In acute liver injury the presence of encephalopathy is required for a diagnosis of fulminant hepatic failure. Encephalopathy happens more commonly in patients with cirrhosis. Gut-derived neurotoxins which are normally detoxified by the liver accumulates in the systemic circulation as detoxification function is lost in cirrhosis due to decreased mass of the liver and vascular shunting occurs. These neurotoxins are responsible for the symptoms of hepatic encephalopathy. Ammonia levels are elevated in CLD patients with hepatic encephalopathy, but the levels of ammonia cannot be used to predict the severity of the disease. Other compounds that are recognized as the development of encephalopathy include false neurotransmitters and mercaptans.

In acute liver failure, mental status changes can occur within weeks to m Cerebral edema is a feature of acute fulminant hepatic failure and does in happen with encephalopathy secondary to CLD .Care should be taken in prevent cerebral herniation and treatment should be instituted to decrease the cerebral edema with mannitol and judicious use of intravenous fluids. Certain factors can precipitate hepatic encephalopathy .These include SBP, hypokalemia, UGI bleed, increased dietary protein load .These factors should be looked for and corrected. Patients may be contsed or exhibit personality changes. They may even be violent and difficult to manage; alternatively patients may be very sleepy and difficult to rouse. The precipitating events

should be sought carefully. If patients have ascites diagnostic tapping to rule out SBP should be done. Any evidence of GI bleed should be sought, and patients should be appropriately hydrated. Electrolyte abnormalities should be corrected. In these patients clinically asterixis should be looked for. Asterixis can be elicited by having the patients extend their arms and bending their wrists backward. In this maneuver, patients who are encephalopathic may have a “liver flap”-i.e. a sudden forward movement of the wrist. This requires patients cooperation with the examiner and so cannot be elicited in those who are severely encephalopathic or in hepatic coma The diagnosis of hepatic encephalopathy is clinical and requires an experience clinician to recognize and put together all of the various features.

Treatment of hepatic encephalopathy includes management of the precipitating factors. Restriction of dietary protein which was considered in the past is now discouraged due to the negative impact it exerts. Vegetable proteins are preferred over animal proteins. The mainstay of treatment is to use lactulose a non-absorbable disaccharide, that causes acidic milieu in the colon and there by converts ammonia into ammonium and prevents the diffusion of ammonia produced in the gut in to portal system. It also alters the gut microbiome to a favorable milieu. The amount of lactulose ingested is titrated to a net result of achieving 2-3 soft stools per day. Antibiotics that are retained in the gut and not absorbed in to systemic circulation are preferred to sterilize the gut. Neomycin and metronidazole were used in the past .Their use became limited due to side effect such as ototoxicity and peripheral neuropathy. The

drug of choice now is Rifaximin at a dosage of 550 mg twice daily. Supplementing Zinc can also be tried.

ABNORMALITIES OF COAGULATION

Coagulopathy is almost universal in patients with cirrhosis. This is because the synthesis of coagulation factors is decreased and anticoagulants clearance from the system is impaired. In addition patients may have thrombocytopenia as a result of hypersplenism due to portal hypertension. Administration of parenteral vitamin K does not improve the clotting factors or the prothrombin time in cirrhosis patients. Platelet function is also abnormal apart from reduction in its number.

BONE DISEASE IN CIRRHOSIS

Osteoporosis can occur in cirrhosis and other liver diseases with predominant cholestatic picture due to Vitamin D malabsorption. The rate of bone resorption exceeds that of new bone formation in patients with cirrhosis, resulting in bone loss. Dual x-ray absorptiometry (DEXA) is a useful method for determining osteoporosis or osteopenia in patients with chronic liver disease. When a DEXA scan shows decreased bone mass, treatment should be administered with bisphosphonates that are effective at inhibiting resorption of bone and efficacious in the treatment of osteoporosis

HEPATORENAL SYNDROME

Hepatorenal syndrome is the term attributed to the renal impairment which develops in patients with end stage liver cirrhosis or those with acute fulminant liver failure which is both reversible and only functional without any anatomical alteration. It is characterized by marked reduction in glomerular filtration rate and renal plasma flow (RPF), without any other contributing cause to renal failure. The pathophysiology behind HRS is severe vasoconstriction in the renal vascular bed with paradoxical peripheral arterial vasodilation. The function of the renal tubules is normal and there is no proteinuria or abnormal histology in the kidneys.

HRS has been classified in to two types

Type 1 HRS is defined as the “acute onset of rapidly progressive oliguric renal failure unresponsive to volume expansion with the doubling of serum creatinine value to more than 2.5 mg/dl within 2 weeks duration”. However as recently proposed a diagnosis of type 1 HRS should be considered whenever there is fulfillment of criteria defining acute kidney injury by an abrupt increase in serum creatinine more than or equal to 0.3 mg/dl or an increase of more than 1.5 times from the baseline. This is to ensure that treatment is not delayed unnecessarily, as baseline creatinine is a predictor of HRS reversal with vasoconstrictors

Type 2 HRS progresses more slowly and the cut off of serum creatinine is 1.5 mg/dl. A precipitating factor frequently is identified in type 1 HRS,

whereas there are no such factors involved in development of type 2 HRS and it clinically manifests as refractory ascites.

Pathophysiology

Hepatorenal syndrome occurs in the end stage of liver cirrhosis .The worsening of the renal function is because of severe vasoconstriction occurring at the level of renal blood vessels. However the cause for the development of this vasoconstriction is not fully understood .It has been suggested that this can be because of the imbalance that slowly starts developing between the renal vasoconstrictors and vasodilators. In type 2 HRS the mechanisms responsible for development of HRS are gradually progressive whereas in type 1 HRS, there is a sudden worsening of the kidney function due to inability of the compensatory mechanisms to maintain the perfusion in the renal arteries. The development of HRS is the end result of the interaction between these pathways:

1. Splanchnic vasodilation with hyper dynamic circulation with consequent renal vasoconstriction;
2. Activation of renal sympathetic nervous system (SNS
3. Cardiac dysfunction that may result in decreased renal pcr&sion.
4. Action of different vasoactive mediators and cytokines renal circulation.

Peripheral Arterial Vasodilation

In patients with cirrhosis and portal hypertension, there is increased production of certain vasodilating factors such as nitric oxide in the splat and to a lesser extent in systemic circulation .This results in splanchnic alt systemic vasodilatation and splanchnic blood pooling as there is also increased resistance to the flow of the portal blood through the fibrosed liver. Thus the effective circulating intravascular volume decreases and this results in stimulation of carotid baroreceptors and thereby increase in the activity of sympathetic nervous system (SNS). This and the decrease in the effective volume of renal blood flow stimulates the renin angiotensin aldosterone system (RAAS). Thus a hyper dynamic circulation results with decreased peripheral vascular resistance and renal vasoconstriction. With progression of cirrhosis, this process becomes a vicious cycle, as with further increase in splanchnic vasodilatation, worsens the renal vasoconstriction.

Stimulation of the Renal SNS

Studies have shown that there are reflexes such as hepato renal reflex that may determine the renal vasoconstriction in response to increased pressure in hepatic sinusoids. This is mediated through the renal sympathetic system.

1) Assay is costlier

2) Assay needs further standardization.

3) The levels may be altered in infection and by drugs such as ACE inhibitors, steroids and calcineurin inhibitors.

4) Cystatin C is also a marker for fibrosis progression in liver cirrhosis. This could represent a possible bias when interpreting the results. Thus its use is still not validated.

Renal Doppler Ultrasonography

Renal vasoconstriction is the major pathology behind I This renal vasoconstriction can be assessed using Doppler ultrasound of the renal arteries by using an index called renal resistive index (RI).This value is derived from the spectral waveforms corresponding to the flow at the renal arteries and is determined using the formula

$$\text{Renal Resistive Index} = \frac{\text{Peak systolic frequency shift - Lowest diastolic frequency shift}}{\text{Peak systolic frequency shift}}$$

RI in cirrhosis is increased when compared to the normal population. And studies have shown that a high RI value (more than 0.7) can be documented in cirrhotic patients even in whom RFT is normal.

It has also been shown that normally RI exhibits a gradient decreasing from the hilum towards the outer cortex. In cirrhotic patients with diuretic responsive ascites this gradient is well maintained. Whereas as the severity increases and in cirrhotic patients with refractory ascites this gradient is lost

and the RI at the level of the cortex measured in interlobular arteries is also high suggesting renal cortex vasoconstriction. This happens even before serum creatinine begins to raise. Thus in cirrhotic patients an increased RI in spite of normal values of serum creatinine, implicates that they are at a greater risk for development of renal dysfunction and elevation of serum creatinine. With treatment of FIRS, RI value reduces. Similarly liver transplantation also decreases the RI. Thus renal RI assessed using Doppler ultrasound may be used as an early marker for renal impairment in cirrhosis patients. However raised RI does not differentiate whether the cause of renal dysfunction is due to vasoconstriction alone or if it is associated with intrinsic kidney damage.

Numerous studies have been conducted to evaluate the use of renal resistive index in cirrhosis patients to identify early renal dysfunction.

Early detection of renal vasoconstriction by Doppler ultrasound predicts future development of HRS in patients with cirrhosis. In a perspective study done by Platt eta! RI. HRS develops in 26% of patients with elevated resistive indices compared with 1% of those with normal indices ($P < 0.001$) and the probability that patients with high RI would subsequently develop HRS is 55%.

LIVER TRANSPLANTATION

Liver transplantation is indicated for end-stage *cirrhosis* of all causes. In *sclerosing cholangitis* and *Caroli's disease* (multiple cystic dilatations of the intrahepatic biliary tree), recurrent infections and sepsis associated with

inflammatory and fibrotic obstruction of the biliary tree may be an indication for transplantation. Because prior biliary surgery complicates,and is a relative contraindication for liver transplantation, surgical diversion of the biliary tree has been all but abandoned for patients with sclerosing cholangitis. In patients who undergo transplantation for *hepatic vein thrombosis (Budd-Chiarisyndrome)*, postoperative anticoagulation is essential; underlying myeloproliferative disorders may have to be treated but are not a contraindication to liver transplantation.

If a donor organ can be located quickly, before life-threatening complications - including cerebral edema set in, patients with acute liver failure are candidates for liver transplantation. Routine candidates for liver transplantation are patients with *alcoholic cirrhosis*, *chronic viral hepatitis*, and *primary hepatocellular malignancies*. Although all three of these categories are considered to be high risk, liver transplantation can be offered to carefully selected patients. Currently, chronic hepatitis C and alcoholic liver disease are the most common indications for liver transplantation, accounting for over 40% of all adult candidates who undergo the procedure. Patients with alcoholic cirrhosis can be considered as candidates for transplantation if they meet strict criteria for abstinence and reform; however, these criteria still do not prevent recidivism in up to a quarter of cases. Patients with chronic hepatitis C have early allograft and patient survival comparable to those of other subsets of patients after transplantation; however, reinfection in the donor organ is universal, recurrent hepatitis C is insidiously progressive, the impact

of antiviral therapy is limited, allograft cirrhosis develops in 20–30% at 5 years, and cirrhosis and late organ failure are being recognized with increasing frequency beyond 5 years. In patients with chronic hepatitis B, in the absence of measures to prevent recurrent hepatitis B, survival after transplantation is reduced by approximately 10–20%; however, prophylactic use of hepatitis B immune globulin (HBIg) during and after transplantation increases the success of transplantation to a level comparable to that seen in patients with nonviral causes of liver decompensation.

The specific oral antiviral drugs lamivudine, adefovir dipivoxil, and entecavir can be used both for prophylaxis against and for treatment of recurrent hepatitis B, facilitating further the management of patients undergoing liver transplantation for end-stage hepatitis B; most transplantation centers rely on a combination of HBIg and antiviral drugs to manage patients with hepatitis B. Patients with nonmetastatic primary hepatobiliary tumors - primary hepatocellular carcinoma (HCC), cholangiocarcinoma, hepatoblastoma, angiosarcoma, epithelioid hemangioendothelioma, and multiple or massive hepatic adenomata - have undergone liver transplantation; however, for some hepatobiliary malignancies, overall survival is significantly lower than that for other categories of liver disease.

Most transplantation centers have reported 5-year recurrence-free survival rates in patients with unresectable HCC for single tumors <5 cm in diameter or for three or fewer lesions all <3 cm comparable to those seen in patients undergoing transplantation for non-malignant indications.

Consequently, liver transplantation is currently restricted to patients whose hepatic malignancies meet these criteria. Expanded criteria for patients with HCC are being evaluated. Because the likelihood of recurrent cholangiocarcinoma is very high, only highly selected patients with limited disease are being evaluated for transplantation after intensive chemotherapy and radiation.

Thus in the current era where biochemical tests for detecting renal dysfunction in cirrhosis at an early stage, is not useful, renal artery Doppler can prove to be an important tool to assess the degree of renal impairment even before the disease manifests biochemically. Thus if picked up at an early stage, steps to prevent further worsening of renal function can be implemented.

MATERIALS AND METHODS

MATERIALS AND METHODS

STUDY POPULATION

SOURCE OF DATA

The study was conducted on 50 consecutive patients admitted to Government Rajaji Hospital & Madurai Medical College during the study period.

Inclusion criteria

Liver cirrhosis patients of any etiology as diagnosed by clinical, biochemical and imaging methods.

Subgroups of patients included

Patients with compensated cirrhosis (absence of ascites,hepatic encephalopathy, upper GI bleed)

Patients with decompensated cirrhosis

Exclusion criteria

Patients with

1. Diabetes
2. Hypertension
3. Nephrotoxic medication intake
4. Acute GI bleeding and shock
5. Ultrasonographic evidence of obstruction or parenchymal renal disease
6. Sepsis

ANTICIPATED OUTCOME

RENAL RESTITIVE INDEX is not inferior in sensitivity and specificity to the MELD/CTP score.

DATA COLLECTION

Informed consent was obtained from all patients/patients caretakers for the study. In all the patients relevant information (detailed history with detailed clinical examination) was collected in a predesigned proforma.

LABORATORY INVESTIGATIONS

a) Complete blood count
b) Liver function test (LFT)
c) Renal function test (RFT)
d) PT-INR
e) Serum albumin
f) Ultrasound abdomen
g) Renal artery duplex Doppler

DESIGN OF STUDY

Hospital based Prospective study.

PERIOD OF STUDY

3 MONTHS (JULY 2017 to September 2017)

COLLABORATING DEPARTMENTS

DEPARTMENT OF MEDICAL GASTROENTEROLOGY

DEPARTMENT OF BIOCHEMISTRY

DEPARTMENT OF RADIOLOGY

ETHICAL CLEARANCE: Clearance obtained.

CONSENT: Individual/caretakers written and informed consent.

ANALYSIS: Statistical analysis will be performed using appropriate tests as required according to data.

CONFLICT OF INTEREST: NIL

FINANCIAL SUPPORT: SELF

PARTICIPANTS:

50 LIVER CIRRHOSIS patients admitted in medical ward at Government Rajaji hospital, Madurai

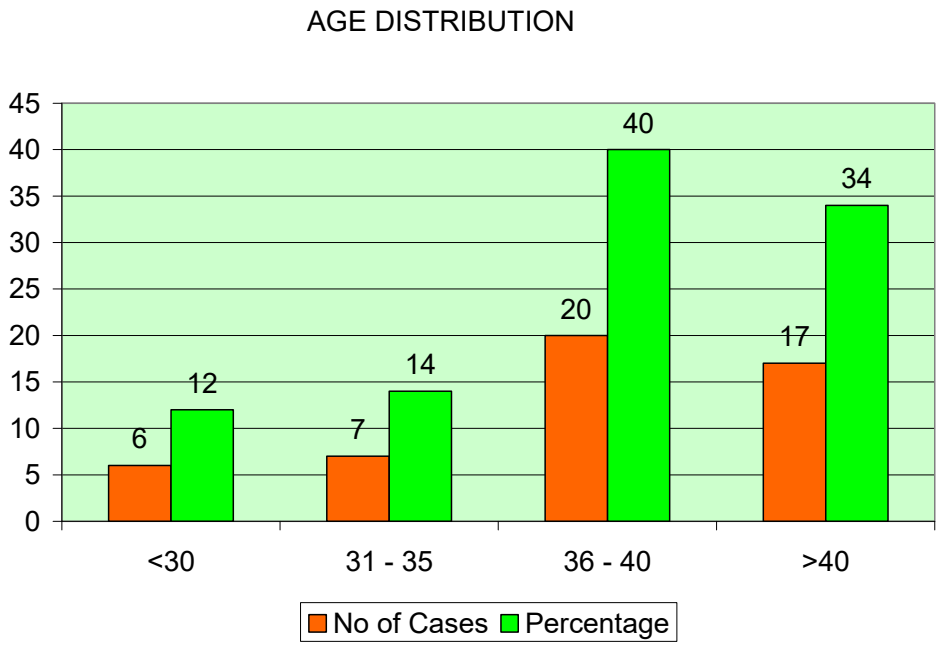
OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

TABLE 1: DISTRIBUTION OF AGE

AGE	No of Cases	Percentage
<30	6	12
31 – 35	7	14
36 – 40	20	40
>40	17	34
Total	50	100
Mean	38.38	
SD	6.46	

CHART 1 AGE DISTRIBUTION IN STUDY POPULATION



COMMENTS

About 40% of the study population were in the group of 36-40 years.

About 34% of the study population were in the group of >40 years.

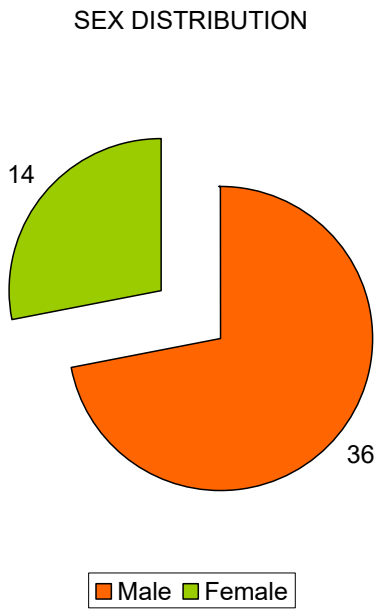
About 14% of the study population were in the group of 31-35 years.

About 12% of the study population were in the group of <30 years.

TABLE 2: SEX DISTRIBUTION IN THE STUDY POPULATION

SEX	No of Cases	Percentage
Male	36	72
Female	14	28
Total	50	100

CHART 2: SEX DISTRIBUTION IN THE STUDY POPULATION



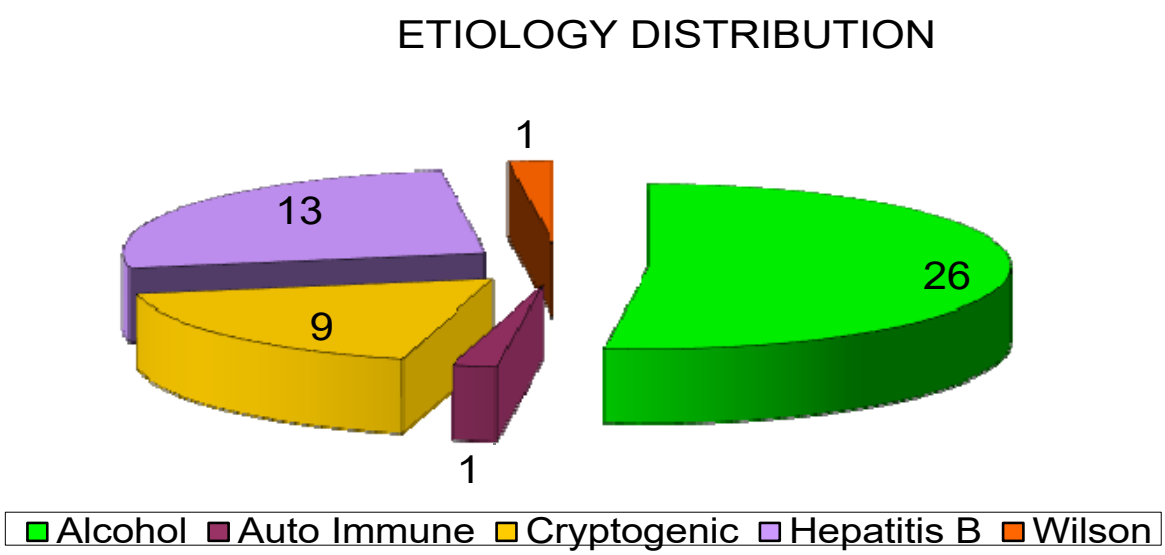
COMMENTS

About 72% of the study population were males and 28% were females.

TABLE 3: ETIOLOGY DISTRIBUTION IN THE STUDY POPULATION

ETIOLOGY	NO OF CASES	PERCENTAGE
Alcohol	26	52
Auto Immune	1	2
Cryptogenic	9	18
Hepatitis B	13	26
Wilson	1	2
Total	50	100

CHART 3



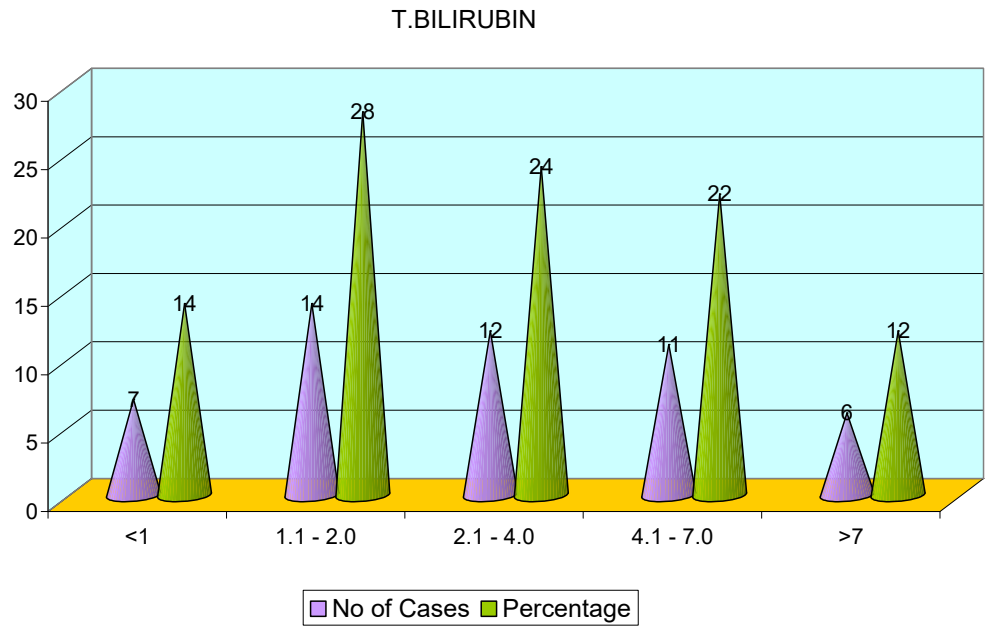
COMMENTS

Alcohol was the most common cause of cirrhosis in the study population (52%).Followed by hepatitis B(26%). Other cyptogenic causes predominate next to alcohol and hepatitis B which was followed by autoimmune hepatitis and Wilson's disease.

TABLE 4: SERUM BILURUBIN IN THE STUDY POPULATION

T.BILIRUBIN	NO OF CASES	PERCENTAGE
<1	7	14
1.1 - 2.0	14	28
2.1 - 4.0	12	24
4.1 - 7.0	11	22
>7	6	12
Total	50	100
Mean	3.56	
SD	3.01	

CHART 4



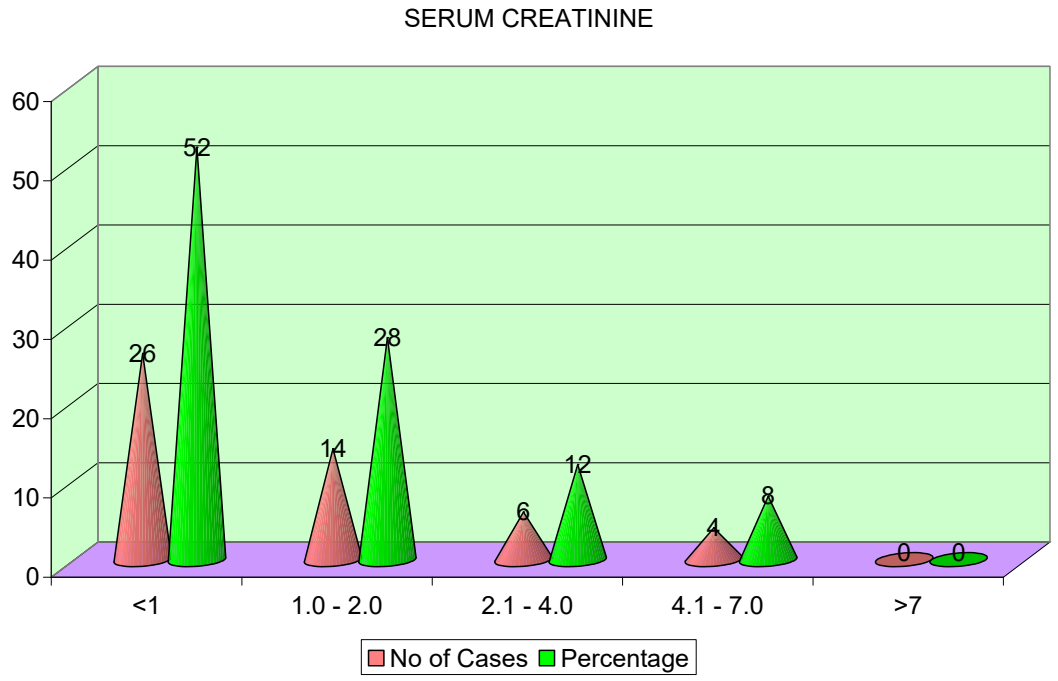
COMMENTS

Mean bilirubin among the study population was 3.56.

TABLE 5: SERUM CREATININE IN STUDY POPULATION

S.CREATININ	No of Cases	Percentage
<1	26	52
1.0 - 2.0	14	28
2.1 - 4.0	6	12
4.1 - 7.0	4	8
>7	0	0
Total	50	100
Mean	1.5	
SD	1.33	

CHART 5



COMMENTS

Mean creatinine among the study population was 1.5.

TABLE 6: PT-INR IN THE STUDY POPULATION

PT INR	No of Cases	Percentage
<1	14	28
1.0 - 2.0	20	40
2.1 - 4.0	10	20
>4.0	6	12
Total	50	100
Mean	1.96	
SD	1.3	

CHART 6

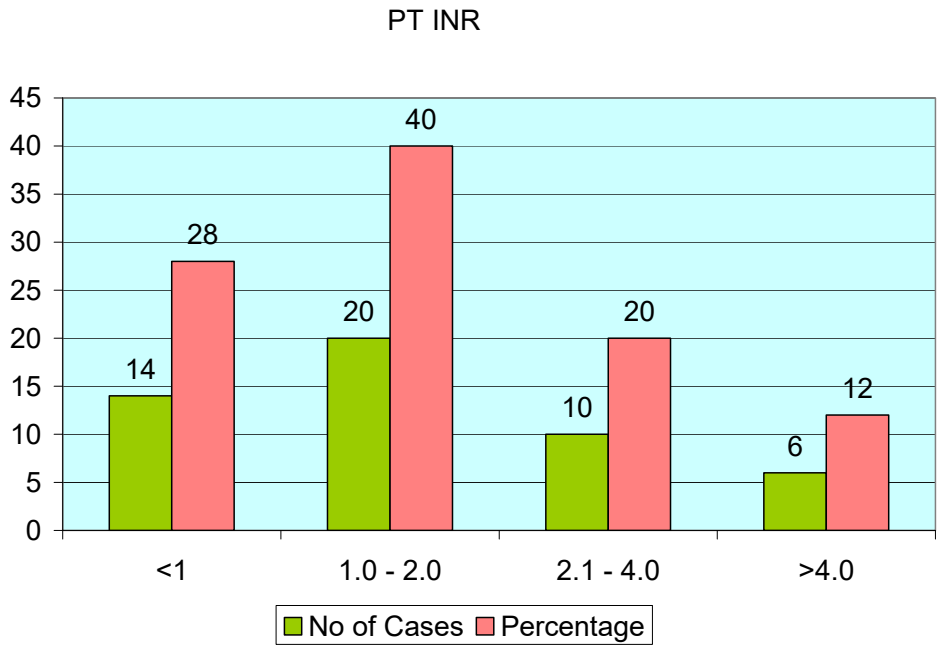


TABLE 7: SERUM ALBUMIN IN THE STUDY POPULATION

ALBUMIN	No of Cases	Percentage
<2	8	16
2.1 - 3.0	18	36
3.1 - 4.0	14	28
>4.0	10	20
Total	50	100
Mean	3.05	
SD	0.92	

CHART 7

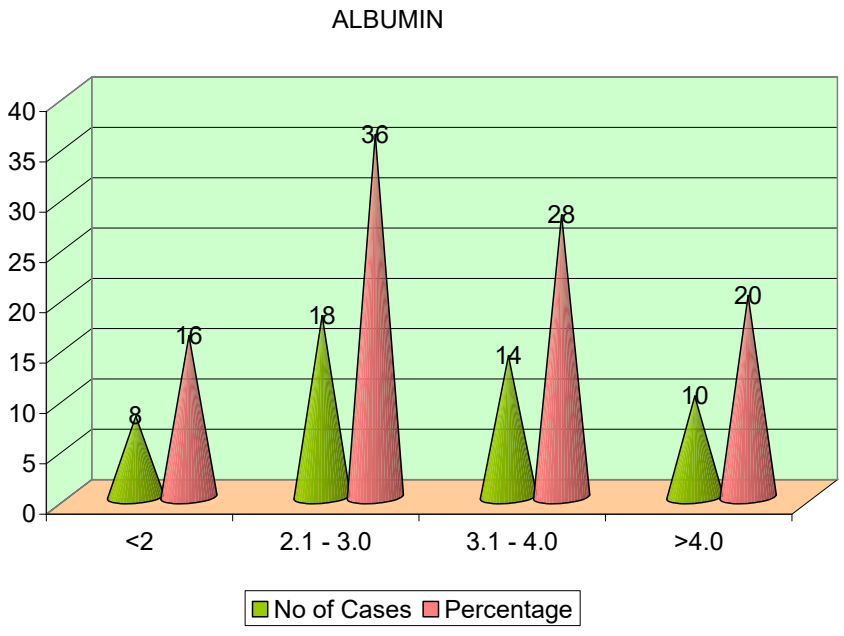
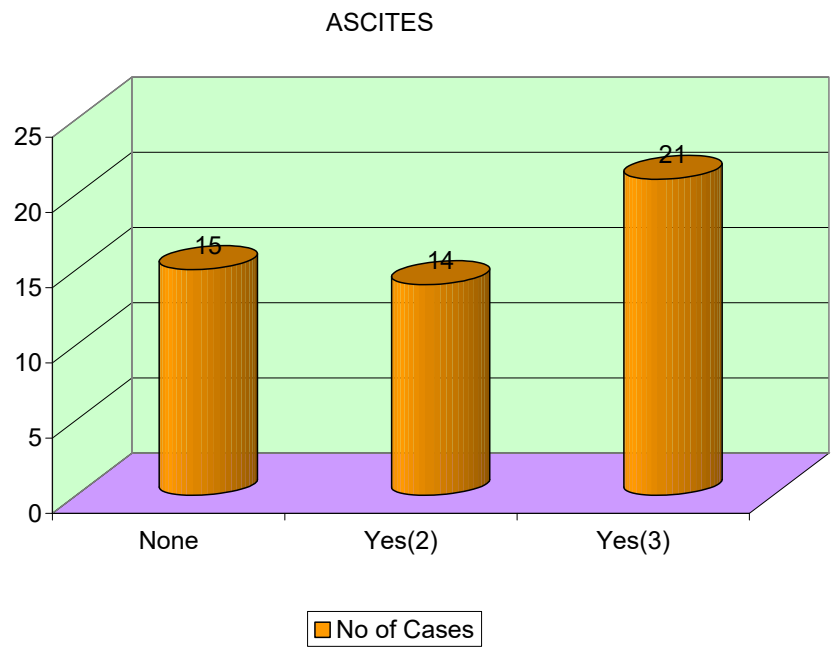


TABLE 8: ASCITES IN THE STUDY POPULATION:

ASCITES	No of Cases	Percentage
None	15	30
Yes(2)	14	28
Yes(3)	21	42
Total	50	100

CHART 8



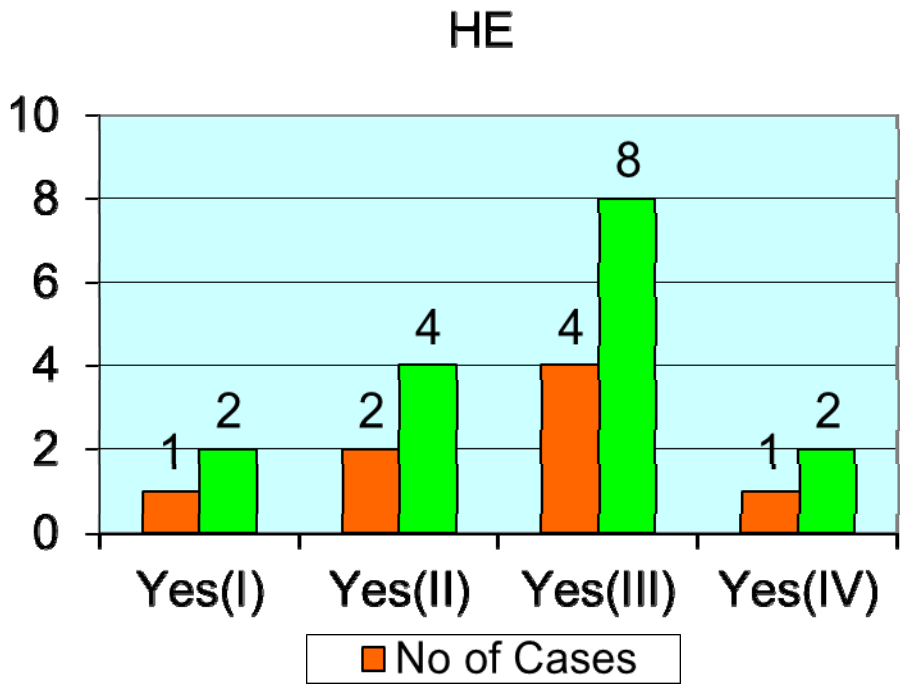
COMMENTS

Around 70% of patients in the study population had ascites.In this 28% of patients had grade 2 ascites according to CTP classification.42% of patients had grade 3 ascites.

TABLE 9: HEPATIC ENCEPHALOPATHY IN THE STUDY POPULATION

Hepatic encephalopathy	No of Cases	Percentage
Yes(I)	1	2
Yes(II)	2	4
Yes(III)	4	8
Yes(IV)	1	2
None	42	84
Total	8	16

CHART 9

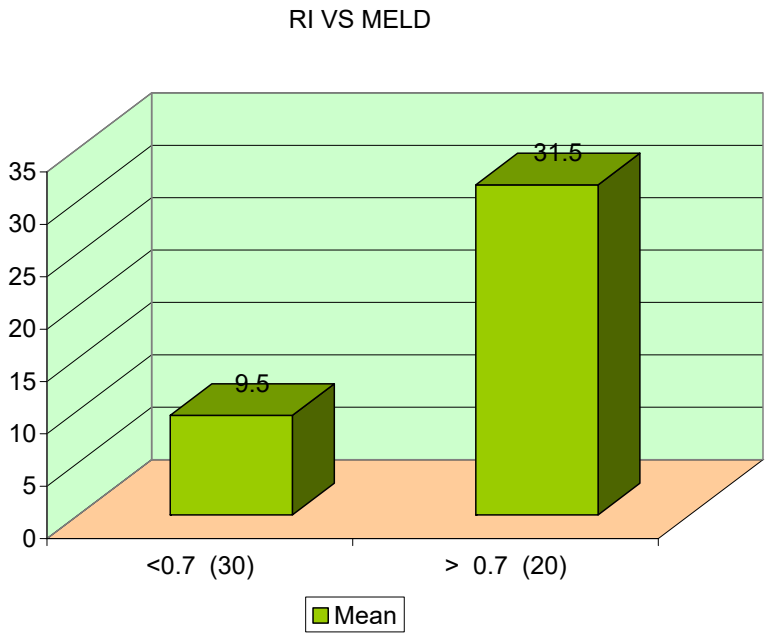


COMMENTS 16% of the total patients had hepatic encephalopathy.8% of patients in grade 3 followed by 4% had grade 2 and 2% in grade 1 and 2% in grade 4 hepatic encephalopathy.

TABLE 10: RESISTIVE INDEX (RI) VS MELD SCORE:

RI	Mean (MELD)	SD
<0.7 (30)	9.5	2.53
> 0.7 (20)	31.5	8.12
p value	<0.001 Sig	
Correlation coefficient		0.903
Very Good correlation between RI and Meld		

CHART 9



COMMENTS

While compared RI with MELD SCORE mean MELD in patients with RI <0.7(30 patients) was 9.5 and in patients with RI>0.7(20 patients) was 31.5. Correlation coefficient was 0.903 indicates very good correlation.p value was <0.001.

TABLE 10: MELD SCORE

MELD	No of Cases	Percentage
<10	15	30
10 - 15	14	28
16 – 25	7	14
26 – 40	11	22
>40	3	6
Total	50	100
Mean	18.32	
SD	12.18	

TABLE 11: CHILD-PUGH SCORE

Child pugh	No of Cases	Percentage
5A	15	30
7B	7	14
8B	4	8
9B	3	6
10C	3	6
11C	1	2
12C	1	2
13C	9	18
14C	3	6
15C	4	8
Total	50	100

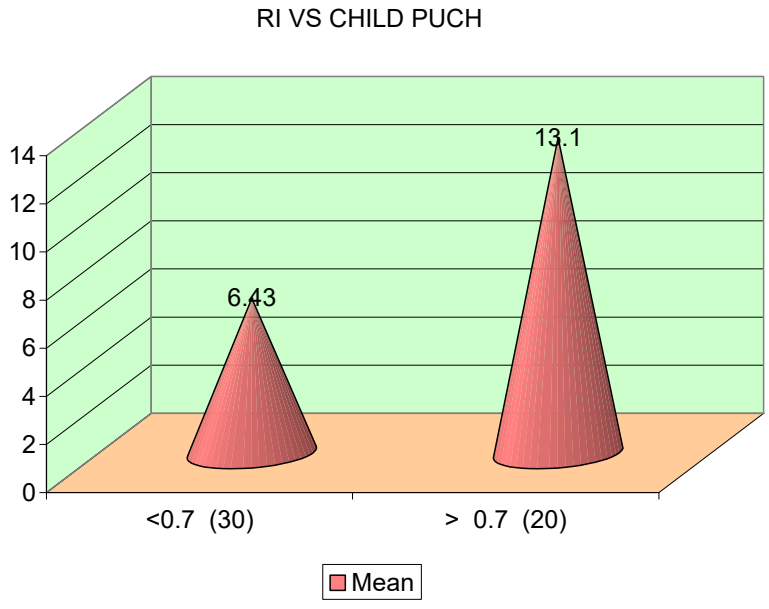
TABLE 12: RENAL RESISTIVE INDEX (RI) VS CHILD-PUGH SCORE

RI	Mean CHILD-PUGH SCORE	SD
<0.7 (30)	6.43	1.61
> 0.7 (20)	13.1	1.48

p value <0.001 Sig

Correlation coefficient	0.873
Very Good correlation between RI and Child pugh	

CHART 10



COMMENTS

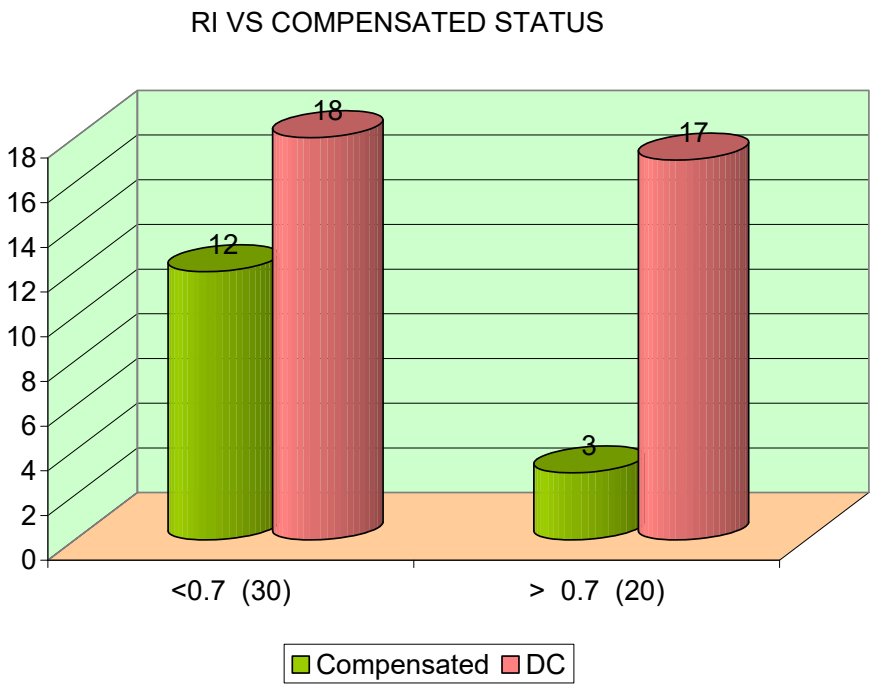
While compared RI with CHILD-PUGH SCORE mean CHILD-PUGH SCORE in patients with RI <0.7(30 patients) was 6.43 and in patients with RI>0.7(20 patients) was 13.1. Correlation coefficient was 0.873 indicates very good correlation.p value was <0.001.

TABLE 13: COMPENSATED VS DECOMPENSATED FORM:

Compensation Status	No of Cases	Percentage
Compensated	15	30
Decompensated	35	70
Total	50	100

RI vs Status	Compensated	DC
<0.7 (30)	12	18
> 0.7 (20)	3	17
3/30 vs 12/30		
p value	<0.001 Sig	

CHART 11



COMMENTS

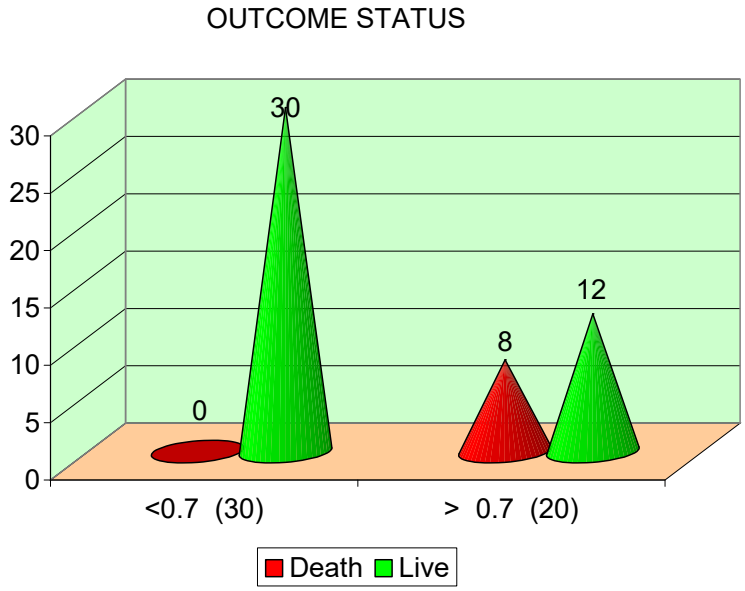
RI was >0.7 in 17 liver cirrhosis patients with DECOMPENSATED FORM while RI >0.7 in only 3 patients with COMPENSATED FORM.P value was <0.001.

TABLE 14: RI IN DEATH VS ALIVE PATIENTS:

Status	No of Cases	Percentage
Death	8	16
Alive	42	84
Total	50	100

RI vs Status	Death	Alive
<0.7 (30)	0	30
> 0.7 (20)	8	12
0/30 vs 8/20		
p value	<0.001 Sig	

CHART 12



COMMENTS

At the end of 3 months of registration, patient's clinical status was reviewed. 8 patients were died.All the 8 patients had RI>0.7.P value was <0.001. RENAL RESISTIVE INDEX correlated strongly with short term in-hospital mortality

DISCUSSION

DISCUSSION

In total 50 patients about 40% of the study population were in the group of 36-40 years. About 34% of the study population were in the group of >40 years. About 14% of the study population were in the group of 31-35 years. About 12% of the study population were in the group of <30 years. About 72% of the study population were males and 28% were females. Alcohol was the most common cause of cirrhosis in the study population (52%).Followed by hepatitis B(26%). Other cyptogenic causes predominate next to alcohol and hepatitis B which was followed by autoimmune hepatitis and Wilson's disease. Mean bilirubin among the study population was 3.56. Mean creatinine among the study population was 1.5.

Around 70% of patients in the study population had ascites.In this 28% of patients had grade 2 ascites according to CTP classification.42% of patients had grade 3 ascites.

16% of the total patients had hepatic encephalopathy.8% of patients in grade 3 followed by 4% had grade 2 and 2% in grade 1 and 2% in grade 4 hepatic encephalopathy.

While compared RI with MELD SCORE mean MELD in patients with RI <0.7(30 patients) was 9.5 and in patients with RI>0.7(20 patients) was 31.5. Correlation coefficient was 0.903 indicates very good correlation.p value was <0.001.

While compared RI with CHILD-PUGH SCORE mean CHILD-PUGH SCORE in patients with RI <0.7(30 patients) was 6.43 and in patients with RI>0.7(20 patients) was 13.1. Correlation coefficient was 0.873 indicates very good correlation.p value was <0.001.

RI was >0.7 in 17 liver cirrhosis patients with DECOMPENSATED FORM while RI >0.7 in only 3 patients with COMPENSATED FORM.P value was <0.001.

At the end of 3 months of registration, patient's status was reviewed. 8 patients were died. All the 8 patients had RI>0.7.P value was <0.001. RENAL RESISTIVE INDEX correlated strongly with short term in-hospital mortality

CONCLUSION

CONCLUSION

RI is not inferior in sensitivity and specificity to the existing hepatic scoring systems like MELD and CTP SCORE.

MELD score is based on easily measured variables (prothrombin time, bilirubin and creatinine).Serum creatinine is an indicator of impaired renal function. However, it has disadvantages as it depends on muscle mass and physical activity. Therefore renal function based on serum creatinine can be overestimated in patients with advanced cirrhosis.

Thus, it is still necessary to develop improved prognostic markers feasible in daily practice.

Our study confirms that the RI, based on sonographic measurements of intrarenal resistance, is an effective,noninvasive, economical functional test that provides useful information for the prognosis and management of cirrhotic patients.

Elevated RIs may even disclose progress of the liver disease before changes in laboratory results.

Therefore, the RI may help identify a subgroup of high-risk patients with a poor prognosis that require special therapeutic care.

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PROFORMA

Name:

Age / Sex:

Occupation:

Presenting complaints

H/O jaundice

H/O abdominal distension/pedal edema

H/O hematochezia/melena/hematemesis

H/O altered sensorium/altered sleep habit

H/O fever

H/O abdominal pain

H/O oliguria/dysuria/hematuria

Past History:

H/o DM, HT, CKD, CVD, DRUG INTAKE, CAD, Thyroid disorders, CLD, renal transplantation and blood transfusion.

PERSONAL HISTORY

Alcohol intake/smoking/high risk behavior

Clinical Examination

General Examination

Consciousness,

Orientation to time, place, person

Pallor,

Jaundice,

Clubbing,

Lymphadenopathy,

Hydration status

Pedal edema

Other signs of hepatocellular failure

Vitals

PR

BP

RR

SpO2

Urine output

Systemic examination

CVS:

RS:

ABDOMEN

Presence of distended and dilated veins

Direction of flow

Free fluid

Hepatomegaly/splenomegaly

CNS:

Laboratory investigations

a) Complete blood count,

b) Renal function test,

c) Liver function test,

d) PT-INR

e) Serum albumin

f) ultrasonography abdomen

g) Renal artery duplex doppler

S.No	Name	Age	Sex	Etiology	T.Bilirubin	S.Creatinin	PT INR	Albumin	Ascites	HE	RI	MELD	Child pugh	status	Status
1	Ramasamy	42	M	alcohol	1.0	0.9	1.1	4.5	None	None	0.64	7	5A	DC	
2	femina	40	F	Alcohol	0.8	0.9	0.9	4.6	None	None	0.58	6	5A	DC	
3	Radha	48	F	Hepatitis B	1.0	1.1	1.1	4.2	None	None	0.57	8	5A	DC	
4	Mohan	42	M	Cryptogenic	1.1	1.0	1.2	4.5	None	None	0.65	9	5A	DC	
5	Rajkumar	36	M	Alcohol	1.2	0.9	1.3	4.4	None	None	0.66	10	5A	C	
6	Kannaiya	37	M	Hepatitis B	1.1	0.8	0.9	3.7	None	None	0.58	7	5A	DC	
7	Ilakkiyakumar	31	M	Alcohol	1.0	0.6	1	4.3	None	None	0.65	6	5A	C	
8	Kanthasamy	40	M	Alcohol	0.6	0.8	1.2	3.7	None	None	0.66	8	5A	C	
9	Irulayee	32	F	Hepatitis B	1.3	1.0	1.1	3.9	None	None	0.64	8	5A	DC	
10	Muthumohan	35	M	Alcohol	1.2	0.8	0.8	4	None	None	0.62	7	5A	C	
11	Kasimayan	35	M	Alcohol	1.3	0.7	1.4	4.1	None	None	0.63	11	5A	DC	
12	Irulappan	46	M	Hepatitis B	1.2	1.1	1.3	4.2	None	None	0.65	11	5A	DC	
13	Aiyasamy	40	M	Alcohol	1.3	0.9	1.2	4.5	None	None	0.64	9	5A	DC	

14	Ragu	42	M	Hepatitis B	0.9	0.7	1	3.6	None	None	0.65	6	5A	C	
15	Vellapan	48	M	Alcohol	0.8	0.8	0.9	4.2	None	None	0.66	6	5A	DC	
16	Rasu	36	M	Alcohol	2.2	1.0	1.2	3.5	Yes(2)	None	0.68	11	8B	DC	
17	Gomathi	40	F	Hepatitis B	1.8	0.9	1.3	3	Yes(2)	None	0.64	12	7B	C	
18	Vellaisamy	38	M	Alcohol	1.5	0.8	0.9	2.8	Yes(2)	None	0.66	8	7B	C	
19	Magesh	31	M	Hepatitis B	2.4	0.7	0.8	2.9	Yes(2)	None	0.65	10	8B	DC	
20	Jeyakumar	32	M	Alcohol	3.6	0.9	1.1	3	Yes(3)	None	0.67	12	10C	C	
21	Muthumari	39	F	Hepatitis B	4.2	1.2	1.2	3.2	Yes(2)	None	0.68	16	9B	DC	
22	Solaiyappan	40	M	Alcohol	2.5	1.1	1.4	3.4	Yes(3)	None	0.64	15	9B	DC	
23	Murugesh	41	M	Hepatitis B	1.1	0.9	1.3	2.8	Yes(2)	None	0.69	10	7B	DC	
24	Muthu	38	M	Alcohol	2.4	0.7	0.9	3.1	Yes(2)	None	0.65	10	8B	C	
25	Kothandaraman	39	M	Alcohol	1.4	0.6	1	3.2	Yes(2)	None	0.67	8	7B	DC	
26	Subburaju	38	M	Alcohol	1.8	0.7	1.3	3	Yes(2)	None	0.68	12	7B	DC	
27	Mariyammal	48	F	cryptogenic	1.2	0.8	1.4	3.1	Yes(2)	None	0.69	11	7B	C	

28	Vignesh	37	M	Alcohol	2.1	0.9	1	3.2	Yes(2)	None	0.68	9	8B	DC	
29	Radhammal	46	F	Cryptogenic	3.2	1.0	0.9	3.5	Yes(2)	None	0.67	11	9B	C	
30	Alagu	39	M	Alcohol	2.4	1.1	1	3.7	Yes(2)	None	0.66	11	7B	C	
31	Raji	19	F	Auto immune	7.0	1.2	3.1	2.1	Yes(3)	Yes(I)	0.74	28	14C	DC	
32	Chokkalingam	30	M	Alcohol	3.2	1.1	2	2.8	Yes(2)	None	0.7	20	10C	DC	
33	Anitha	28	F	Cryptogenic	7.8	1.0	3.4	2.2	Yes(3)	None	0.74	28	13C	DC	
34	Jothi	30	F	Hepatitis B	14.2	0.9	5.8	2.1	Yes(3)	Yes(III)	0.76	36	15C	DC	Death
35	Nageshwaran	32	M	Alcohol	10.8	0.8	4.2	2	Yes(3)	Yes(III)	0.71	31	15C	DC	Death
36	Muniyammal	37	F	Cryptogenic	4.4	0.7	2.6	3	Yes(3)	None	0.72	23	12C	DC	
37	Logappan	36	M	Alcohol	2.5	0.8	1.8	2.9	Yes(3)	None	0.7	16	10C	C	
38	Veeran	25	M	Wilson	3.5	0.9	2.9	2	Yes(3)	None	0.71	23	13C	DC	
39	Ballayya	41	M	Cryptogenic	4.2	1.0	3	2.1	Yes(3)	None	0.73	24	13C	C	
40	Lingappan	43	M	Alcohol	6.5	1.1	4.8	2.2	Yes(3)	Yes(II)	0.74	32	14C	DC	Death
41	Pandiselvi	41	F	Hepatitis B	5.9	4.5	3.2	1.5	Yes(3)	None	0.77	39	14C	DC	Death

42	Neppolian	46	M	Alcohol	8.5	2.6	4.8	2.2	Yes(3)	Yes(III)	0.79	41	13C	DC	
43	Karthik	39	M	Cryptogenic	5.4	3.6	2.9	2.1	Yes(3)	None	0.8	37	13C	C	
44	Rasukutty	49	M	Alcohol	8.5	2.9	4.2	1.7	Yes(3)	None	0.76	41	13C	DC	
45	Alagukannu	48	F	Hepatitis B	7.0	6.2	3.2	1.6	Yes(3)	None	0.77	40	13C	DC	Death
46	Vaitheeswaran	39	M	Alcohol	3.5	3.7	0.9	1.8	Yes(3)	None	0.78	24	11C	DC	
47	Kadhar baasha	44	M	Hepatitis B	6.0	5.3	3.2	2.2	Yes(3)	None	0.81	39	13C	DC	Death
48	Alex	48	M	Alcohol	5.5	2.8	1.6	1.9	Yes(3)	Yes(IV)	0.79	28	13C	DC	
49	Veeralakshmi	39	F	Cryptogenic	6.5	4.2	3	1.8	Yes(3)	Yes(II)	0.82	39	15C	DC	Death
50	Dhanapal	29	M	Cryptogenic	7.8	3.5	4.2	2.4	Yes(3)	Yes(III)	0.8	42	15C	DC	Death

MADURAI MEDICAL COLLEGE
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ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.P.Anand
Course	:	PG in MD., General Medicine
Period of Study	:	2015-2018
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	Intrarenal resistive index as a prognostic parameter in patients with Liver cirrhosis compared with other Hepatic scoring systems
Ethical Committee as on	:	27.07.2017

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary Chairman Dean / Convenor

Prof Dr V Nagaraajan
M.D., MNAMS, D.M., Dsc.,(Neuro), Dsc (Hon)
CHAIRMAN
IEC - Madurai Medical College
Madurai

DEAN
Madurai Medical College
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URKUND

Urkund Analysis Result

Analysed Document: Dr.Anandh.doc (D31122078)
Submitted: 10/8/2017 9:51:00 PM
Submitted By: stanandy89@gmail.com
Significance: 2 %

Sources included in the report:

1-final work.docx (D31042103)
e309691e-b23b-4986-9a2f-2eed65fae8b0

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